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The Experimental Production of Anaphylactic Pulmonary Lesions with the Basic Characteristics of Rheumatic Pneumonitis. JOHN E. GREGORY AND ARNOLD R. RICH 1

The Relation of the Degree of Sensitivity to Tuberculin to the Persistence of Sensitivity and to Prognosis in Young Children. LYDIA B. EDWARDS, M.D. AND JANET B. HARDY, M.D..... 13

Studies on Acute Schistosomiasis Japonica in the Philippine Islands. I. A Clinical Study of 337 Cases with a Preliminary Report on the Results of Treatment with Fuadin in 110 Cases. MAJOR FREDERICK T. BILLINGS, LIEUT. COLONEL WALTER L. WINKENWERDER, AND CAPTAIN ARNE V. HUNNINEN..... 21

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THE EXPERIMENTAL PRODUCTION OF ANAPHYLACTIC PULMONARY LESIONS WITH THE BASIC CHARACTERISTICS OF RHEUMATIC PNEUMONITIS

JOHN E. GREGORY AND ARNOLD R. RICH

From the Department of Pathology, The Johns Hopkins University Medical Schoo

The clinical recognition of a peculiar type of pneumonitis occurring in some cases of acute rheumatic fever dates from the publications of Latham (1) and Fuller (2) in the middle of the last century. In more recent years, the observations of numerous writers, among them Eiman and Gouley (3, 4, 5), Epstein and Greenspan (6), Rich and Gregory (10) and Neubuerger and his coworkers (7), have definitely characterized the pathological features of the lesions.

The specific nature of these lesions can be recognized only under the microscope. Briefly, the changes consist primarily in focal damage to the small blood vessels, particularly the alveolar capillaries. Slight damage results in exudation of fluid from the capillaries. More severe damage results in haemorrhage. Focal plugging of capillaries with fibrinous or hyaline thrombi is common, and thrombosis of occasional minute veins may also be found. Focal infiltration of alveolar walls with leucocytes may occur, and leucocytes may escape into the alveoli. The leucocytic exudate is ordinarily scanty, and much less dense than in bacterial pneumonias, though in small focal areas involving one or several alveoli the exudate may be rich in leucocytes. In some areas coagulation and inspissation of the fluid may produce a hyaline membrane that lines the respiratory bronchiole and its alveoli. In severe damage the alveolar wall may become necrotic. In later stages, organization of the blood or exudate may occur, with the formation of the so-called "Masson bodies" (7), which are not specific for rheumatic pneumonitis, but may occur in any condition in which focal intra-alveolar organization, particularly of blood or inspissated fibrin, takes place. No bacteria can be demonstrated in the tissues either by culture or stain.

The lesions are decidedly focal, frequently involving only a small segment of a vessel. Confluent foci, however, may result in considerable areas of involvement.

We have previously shown that focal lesions, histologically like those of rheumatic pneumonitis, occur in the lungs of non-rheumatic patients who develop anaphylactic reactions to the sulfonamides (10). This basic identity of the pulmonary lesions of rheumatic fever with those resulting from anaphylactic hypersensitivity in man, in addition to our experimental demonstration that lesions strikingly similar to those of rheumatic carditis occur in rabbits subjected to anaphylactic "serum sickness" (11, 12), led us to study carefully the lungs of animals used in experiments of the latter type. The purpose of the present paper is to illustrate the findings of that study, and so to add the weight of an additional experimental observation to the evidence already accumulated in support of the view that the lesions of rheumatic fever are due to hypersensitive reactions.

The details of procedure in the experimental production of "serum sickness" by means of horse serum, and the reactions of the animals thereto, have been reported previously (9). In addition to the use of horse serum alone as the sensitizing agent, some of the animals in the present series were sensitized to egg albumin, and some to a mixture of horse serum and egg albumin. The egg albumin was prepared by filtering a saturated solution of Merck's powdered "Egg Albumin", in normal saline, through several layers of gauze, and centrifugalizing to free it from undissolved particles. Such a solution was found to contain, on chemical analysis, 6.25 grams percent of protein, of which 5.00 grams percent were albumin.

The antigen was administered intravenously. Each injection, whether of sterile horse serum[1], egg albumin, or equal parts of serum and egg albumin, amounted to approximately 10 cc. per kilogram, except in the case of series PN2 which received 15 cc. per kilo. The number of injections, the survival times, and other pertinent data are shown in Table I.

Sections of the lungs of 56 rabbits were studied. Thirty-eight of the 56 had been injected with serum, 12 with egg albumin, and 6 with a mixture of equal parts of serum and egg albumin. The sections of the lungs of 10 rabbits showed definite lesions. Three of the 10 had been sensitized with serum, one with a mixture of serum and egg albumin, and six with egg albumin alone.

[1]The horse serum was kindly furnished by the Medical Research Division of Sharp and Dohme, Inc.

The pulmonary lesions present in these animals exhibit, in varying degree, focal capillary damage of the type that characterizes the pneumonitis of acute rheumatic fever and of sulfonamide hypersensitivity in man (Figs. 1 to 11). As may be seen in Table I, capillary thrombosis, focal oedema and haemorrhage were the most frequent

TABLE I

RABBIT	SENSITIZING ANTIGEN	AMOUNT GIVEN	TIMES GIVEN	DURATION OF EXPERIMENT	TIME BETWEEN LAST INJECTION AND DEATH	PULMONARY LESIONS					
						Capillary thrombi	Leucocytic infiltration alveolar walls	Necrotic cells in alveolar walls	Focal Intra-alveolar Exudate: Leucocytes	Focal Intra-alveolar Exudate: Oedema	Focal hemorrhage
		cc/kg.		*days*							
13	Horse serum	10 1 2	2 1 1	35	1 day—K*	+	+	+	+	+	–
R48PN2	Horse serum	15	2	46	10 days—K	+	+	–	–	+	–
R61PN3	Horse serum	10	2	28	9 days—K	+	–	–	–	–	–
R92PN6	Egg albumin	10	6	105	Several hours—D	+	–	–	–	+	+
R94PN6	Egg albumin	10	6	105	24 hours—D	+	–	–	–	+	+
R95PN6	Egg albumin	10	6	105	24 hours—D	+	–	–	–	–	–
R99PN6	Egg albumin	10	6	105	Several hours—D	+	–	–	–	–	–
R268PN7	Egg albumin	10	2	28	Acute shock—D	+	–	–	+	+	+
R274PN7	Egg albumin	10	3	40	Acute shock—D	+	–	–	–	+	+
R294PN8	Horse serum and egg albumin equal parts	10	2	64	4 days—D	–	–	–	+	+	+

* K, killed; D, died.

lesions. In only one animal was suggestive hyaline membrane formation encountered.

It may be mentioned that in 1932 Vaubel (13), in a study of the effects of hypersensitivity to foreign serum, listed in his protocols the occurrence of thrombosis of pulmonary capillaries and small veins with accompanying oedema in three of sixteen rabbits treated with repeated injections of horse serum intravenously. He did not relate this finding to rheumatic pneumonitis. He regarded the thrombi as being the

result of the fatal anaphylactic shock which the three animals suffered. In one of our animals, too, focal thrombosis of small pulmonary veins was observed. This is likewise an occasional finding in human rheumatic pneumonitis. It should be stated that none of the capillary thrombi in our animals consisted of aggltuinated erythrocytes, and that the thrombi occurred in three animals that did not die of anaphylactic shock (13, R48PN2, R61PN3, Table I).

DISCUSSION

In the experimental animals that form the basis for this report, there have occurred anaphylactic pulmonary lesions that are of the same basic type as those seen in rheumatic pneumonitis. These lesions consist of focal damage to the alveolar capillaries, with attendant capillary thrombosis, exudation and haemorrhage. Gouley and Eiman (4, 5), Epstein and Greenspan (6) and Rich and Gregory (10) have stressed this initial capillary damage in the lesions of human rheumatic pneumonitis.

It is well recognized that capillary damage, varying from increased permeability to endothelial necrosis with haemorrhage or thrombosis, is a characteristic of anaphylactic reactions wherever antigen and antibody meet in vascular tissues (14). Focal capillary damage is, of course, the basis of lesions such as urticarial wheals and purpura, that occur when antigen circulates in the blood of the anaphylactically sensitized body. In previous papers (8, 9, 22) we have shown that, in man and in experimental animals, focal arterial lesions of the periarteritis nodosa type also result from anaphylactic hypersensitivity; and that pulmonary lesions, histologically quite like those of rheumatic pneumonitis, may occur in association with periarteritis nodosa in non-rheumatic subjects (16). The clinical aspects of rheumatic pneumonitis (its sudden focal appearance, and fleeting, migratory character, as emphasized by Coburn (15) and others) are duplicated by the pneumonitis of periarteritis nodosa (17, 21); and these aspects conform with the characteristics of focal anaphylactic lesions such as urticaria and purpura. Cutaneous urticaria and purpura are, of course, familiar in rheumatic fever. Clinically and pathologically, rheumatic pneumonitis has the aspects of urticaria and purpura of the pulmonary capillaries. It is pertinent to the matter in hand that

Harkavy (18), Cole and Korns (19), Vaughan and Hawks (20) and others have described, clinically, precisely similar fleeting pulmonary infiltrations in anaphylactic conditions such as asthma, urticaria and purpura, and angioneurotic oedema. It is altogether probable that Loeffler's syndrome, which is characterized by transitory pulmonary infiltrations associated with eosinophilia and sometimes with other evidences of allergy, represents pathologically the same type of pneumonitis.

In former studies (11, 12) we have shown that lesions with the basic characteristics of rheumatic carditis and arteritis can be produced experimentally by anaphylactic hypersensitivity, and that anaphylactic pneumonitis caused by drug hypersensitivity in man has the basic characteristics of rheumatic pneumonitis (10). In this report we add the experimental production of anaphylactic pulmonary lesions which, in their basic characteristics, are of the type seen in rheumatic fever, to the accumulating evidence in favor of the view that the lesions of rheumatic fever, in whatever part of the body they may occur, are dependent upon anaphylactic hypersensitivity. We have also observed arthritis in animals subjected to serum sickness. This will be described and illustrated in a later paper.

SUMMARY

Sections from the lungs of 56 rabbits, subjected to the serum sickness type of hypersensitive reaction were studied. In 10 of the animals there occurred small focal lesions characterized by damage to the alveolar capillaries (thrombosis, exudation of fluid and cells, haemorrhage) that, in their basic nature, resemble the lesions of rheumatic pneumonitis.

In preceding papers we have shown that cardiac and arterial lesions comparable, in their basic pathological features, with those of rheumatic fever, can be produced experimentally by anaphylactic hypersensitivity, and that anaphylactic pneumonitis in man (sulfonamide hypersensitivity) has the histological characteristics of rheumatic pneumonitis. The present experimental evidence is offered as further support of the view that the various lesions of rheumatic fever are the results of hypersensitivity.

REFERENCES

1. LATHAM, P. M.: Lectures on Clinical Medicine. London, 1846, **I,** p. 85.
2. FULLER, H. W.: On Rheumatism. New York, F. and W. Wood, 1854, p. 249.
3. EIMAN, J., AND GOULEY, B. A.: Rheumatic pneumonitis. Arch. Path., 1928, **5,** 558.
4. GOULEY, B. A., AND EIMAN, J.: The pathology of rheumatic pneumonia. Amer. J. Med. Sc., 1932, **183,** 359.
5. GOULEY, B. A.: The evolution of the parenchymal lung lesion in rheumatic fever. Amer. J. Med. Sc., 1938, **196,** 1.
6. EPSTEIN, E. Z.,AND GREENSPAN, E. B.: Rheumatic pneumonia. Arch. Int. Med., 1941, **68,** 1074.
7. NEUBUERGER, K. T., GEEVER, E. F., AND RUTLEDGE, E. K.: Rheumatic pneumonia. Arch. Path., 1944, **37,** 1.
8. RICH, A. R.: The rôle of hypersensitivity in periarteritis nodosa, as indicated by seven cases developing during serum sickness and sulfonamide therapy. Bull. Johns. Hopkins Hosp., 1942, **71,** 123.
9. RICH, A. R., AND GREGORY, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. Bull. Johns Hopkins hosp., 1943, **72,** 65.
10. RICH, A. R., AND GREGORY, J. E.: On the anaphylactic nature of rheumatic pneumonitis. Bull. Johns Hopkins Hosp., 1943, **73,** 465.
11. RICH, A. R., AND GREGORY, J. E.: Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. Bull. Johns Hopkins Hosp., 1943, **73,** 239.
12. RICH, A. R., AND GREGORY, J. E.: Further experimental cardiac lesions of the rheumatic type produced by anaphylactic hypersensitivity. Bull. Johns Hopkins Hosp., 1944, **75,** 115.
13. VAUBEL, E.: Die Eiweissüberempfindlichkeit (Gewebshyperergie) des Bindesgewebes. Ziegl. Beitr., 1932, **89,** 374.
14. RICH, A. R.: The significance of hypersensitivity in infections. Physiol. Rev., 1941, **21,** 70.
15. COBURN, A. F.: The Factor of Infection in the Rheumatic State. The Williams & Wilkins Co., Baltimore, 1931, pp. 35-41.
16. RICH, A. R.: The rôle of hypersensitivity in the pathogenesis of rheumatic fever and periarteritis nodosa. Proc. Institute of Medicine of Chicago, 1945, **15,** 270.
17. ELKELES, A.: Serial röntgenograms of the chest in periarteritis nodosa as an aid to diagnosis. Brit. Jour. Radiology, 1944, **17,** 368.
18. HARKAVY, J.: Pathogenesis of bronchial asthma with recurrent pulmonary infiltrations and eosinophilic polyserositis. Arch. Int. Med., 1941, **67,** 709.
19. COLE, J., AND KORNS, H. M.: Visceral manifestations of angioneurotic edema; report of a case with recurrent pulmonary involvement. Jour. Allergy, 1933, **5,** 347.

20. VAUGHAN, W. T., AND HAWKS, E. K.: Angioneurotic edema with some unusual manifestations. Jour. Allergy, 1931, **2,** 125.
21. WIER, D. R.: Polyarteritis nodosa. Am. J. Path., 1939, **15,** 79.
22. RICH, A. R.: Hypersensitivity to iodine as a cause of periarteritis nodosa. Bull. Johns Hopkins Hospital, 1945, **77,** 43.

EXPLANATION OF ILLUSTRATIONS

FIG. 1. Thrombus in alveolar capillary in human rheumatic pneumonitis (Aschoff bodies in heart. Autopsy 18944).

FIG. 2. Thrombus in alveolar capillary in rabbit R92PN6 (See Table I).

FIG. 3. Thrombus in alveolar capillary in human rheumatic pneumonitis (same case as Fig. 1).

FIG. 4. Thrombus in alveolar capillary, and intra-alveolar oedema in rabbit R61PN3 (See Table I).

FIG. 5. Thrombus in alveolar capillary in rabbit R94PN6 (See Table I).

FIG. 6. Necrosis of alveolar wall in human rheumatic pneumonitis (Aschoff bodies in heart. Autopsy 18271).

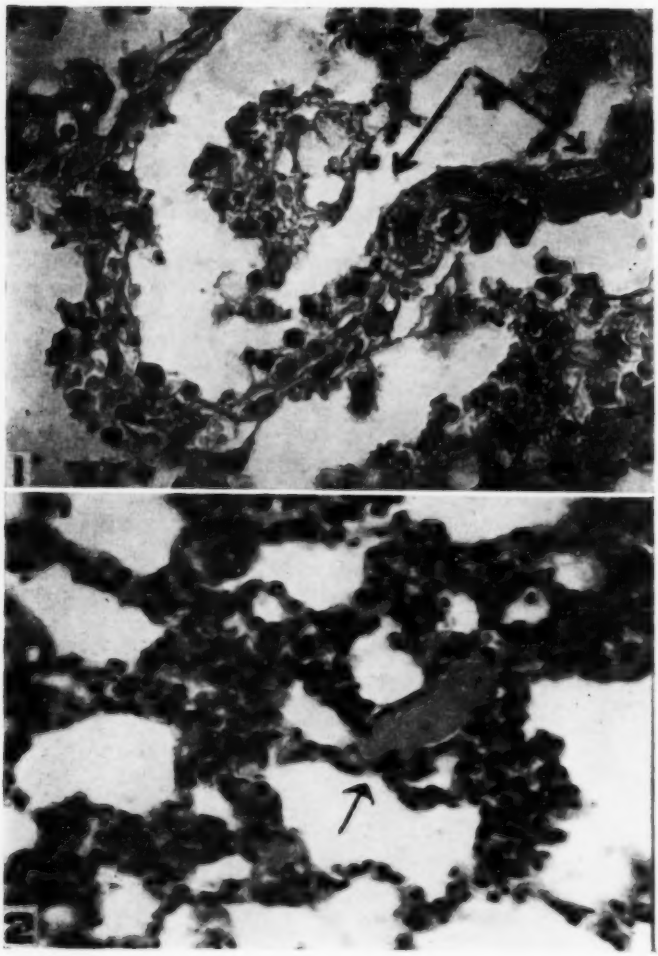
FIG. 7. Necrosis of alveolar wall in rabbit 13 (See Table I. Cardiac lesions of rheumatic type in this animal are illustrated in reference 11).

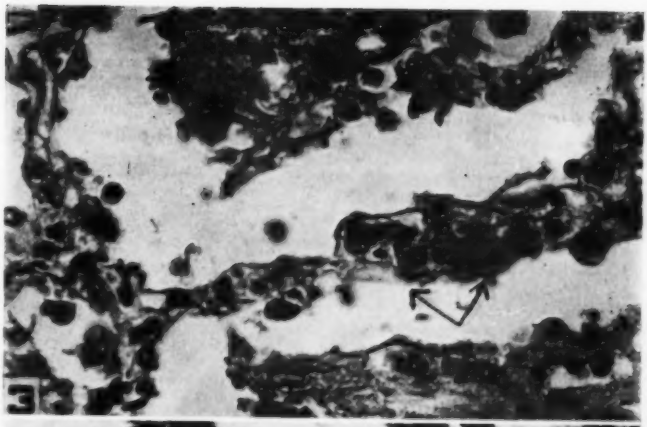
FIG. 8. Focal intra-alveolar exudate in human rheumatic pneumonitis (same case as Fig. 6).

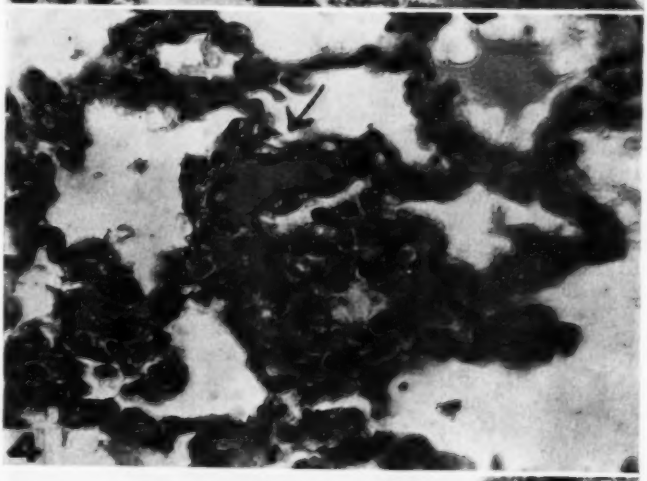
FIG. 9. Focal intra-alveolar exudate in rabbit 13 (same animal as Fig. 7).

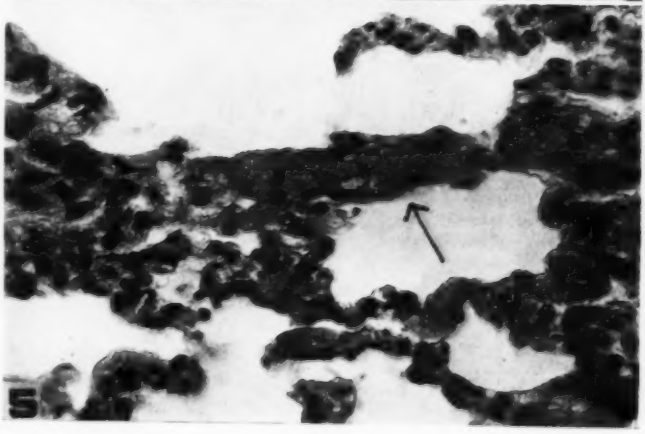
FIG. 10. Focal intra-alveolar haemorrhage and oedema in human rheumatic pneumonitis (Aschoff bodies in heart. Autopsy 16401).

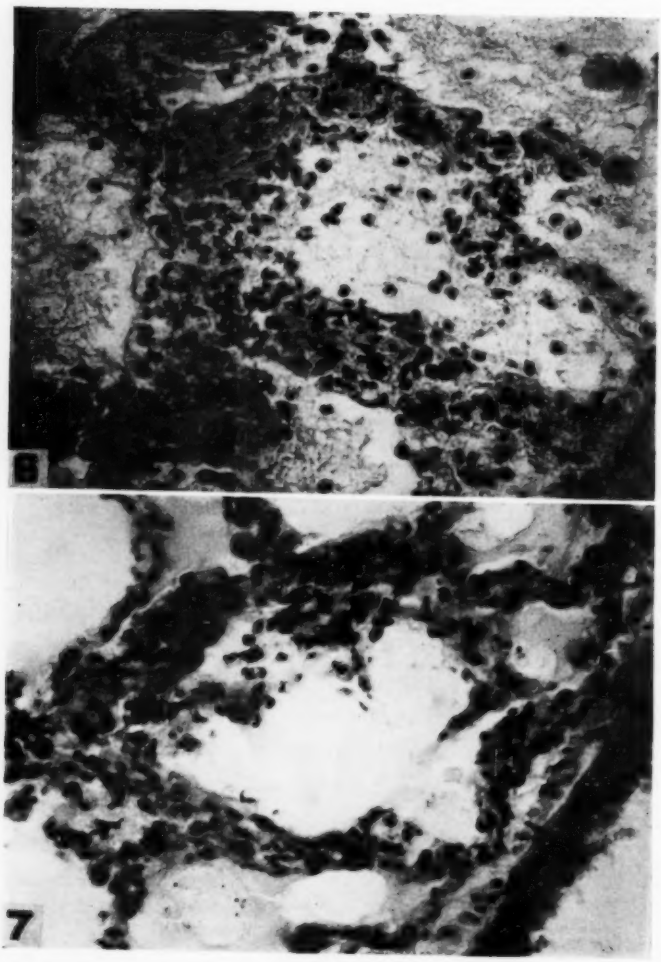
FIG. 11. Focal intra-alveolar haemorrhage and oedema in rabbit R68PN7 (See Table I).







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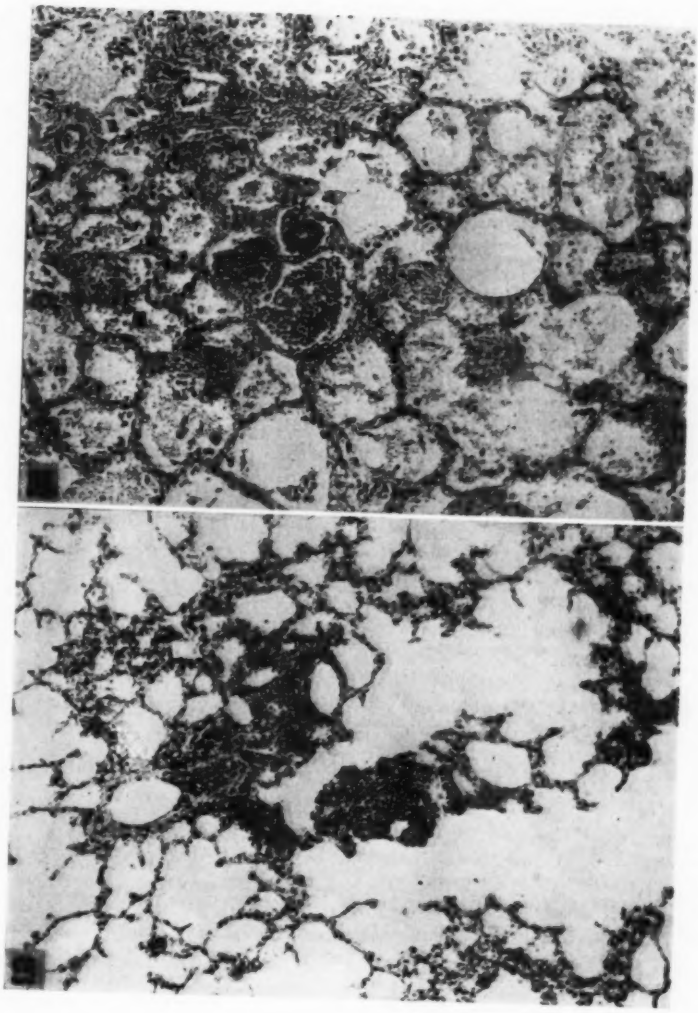

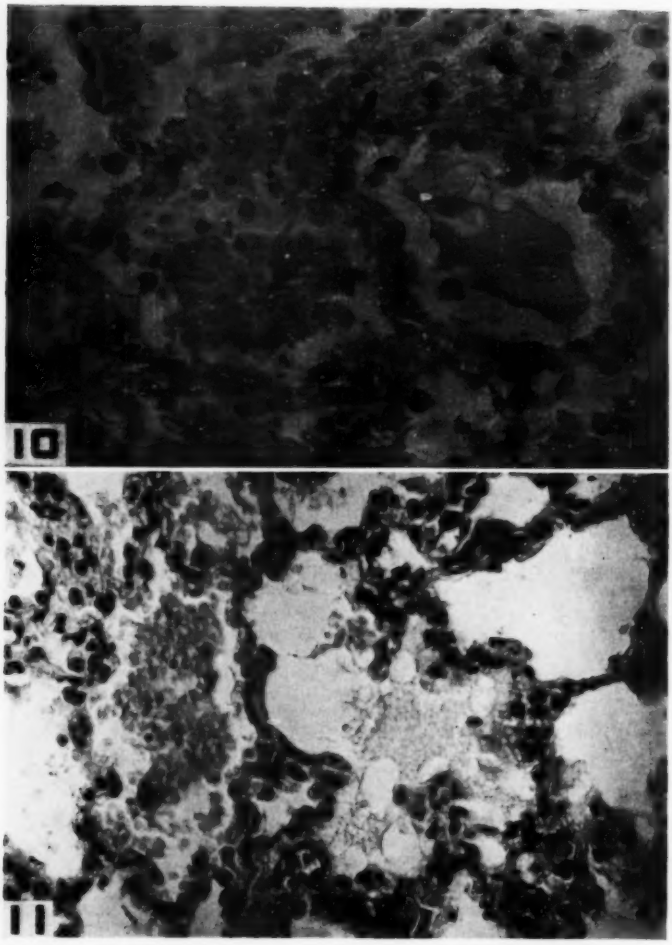
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THE RELATION OF THE DEGREE OF SENSITIVITY TO TUBERCULIN TO THE PERSISTENCE OF SENSITIVITY AND TO PROGNOSIS IN YOUNG CHILDREN[1]

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AND

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It is generally recognized that the discovery, in an infant, of sensitivity to tuberculin carries with it a grave prognosis. There has been, in recent years, in the Tuberculosis Clinic of the Harriet Lane Home, a growing impression that, in the absence of overwhelming tuberculous disease, the prognosis in young children is related in some measure to the degree of hypersensitivity to tuberculo-protein exhibited by the patient. The present study was undertaken to test the validity of this feeling. This study consists of a comparison of the course of tuberculous disease in those patients who, during infancy, reacted only to large doses of tuberculin and in those who were highly sensitive to tuberculin.

The material to be presented is drawn from the records of children followed in the Tuberculosis Clinic of the Harriet Lane Home. This clinic has been in operation since 1928. The criteria for admission to the clinic demand that the child be less than two years of age, and that he be either infected with tuberculosis, as demonstrated by a positive tuberculin test, or known to be exposed to sputum-positive tuberculosis, (usually a house-hold contact), and therefore in unusual danger of becoming infected.

In the routine operation of the clinic, children are tested with tuberculin and x-ray films of their chests are taken upon admission. Both procedures are repeated as indicated at intervals thereafter, and about once each year after the acute stage of their disease is passed. Careful family studies have been made and in most instances accurate informa-

[1] From the Department of Pediatrics, Johns Hopkins University School of Medicine, the School of Hygiene and Public Health, and the Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Maryland. This study was aided by a grant from the Commonwealth Fund, and by the Maryland Tuberculosis Association.

tion as to the degree, type, and duration of exposure to tuberculosis suffered by the registered child is available.

Old tuberculin, made from virulent human strains of tubercle bacilli by the Gilliland Laboratory, Marietta, Pennsylvania, has been used exclusively for skin testing. All tests are performed by the intradermal injection of 0.1 cubic centimeter of solution. The tests are read forty-eight to seventy-two hours after injection. Only such reactions as show one centimeter or more of induration are considered positive. Reactions consisting in erythaema alone or in smaller areas of induration are considered negative. Control tests are done where false positive reactions are suspected. Those patients suspected of having tuberculosis are tested first with 0.001 or 0.01 milligrams of tuberculin and if negative reactions are obtained the dose is increased until a negative reaction to 1.0 milligrams is obtained. Doses larger than this are seldom used. Where the disease is not suspected 0.1 milligrams may be used as an initial dose and the exact level of sensitivity subsequently determined. All patients followed for a period of less than two years have been discarded from this study, with the exception of those who died. It has been demonstrated by Brailey[2] that the great majority of deaths resulting from a primary tuberculous infection occur within the first year after infection. It takes an average of twelve to eighteen months after the onset of infection for calcium deposits to become visible on x-ray films.

This paper deals with a comparison of three groups of patients, all less than two years of age when first observed; all reacting positively to tuberculin by their third birthday; all subsequently re-tested with tuberculin and showing no increase in hypersensitivity within one year after first test; and except for those dying of tuberculosis during the period of study, all followed for two years or more. The three groups are as follows:

I. Those shown to be positive to not less than 1.0 milligram of tuberculin.

II. Those shown to be positive to 0.1 milligram of tuberculin but not less.

[2] Brailey, Miriam: Mortality in Tuberculin-positive Infants. The Millbank Memorial Fund Quarterly, Vol. XV, No. 1, January 1937.

III. Those shown to be positive to 0.01 milligram or less of tuberculin.

With the third group are also included forty-four children who presented a "four plus", i.e., a vesiculated reaction, to 0.1 milligram of tuberculin when first tested and who, because of hospitalization in sanatoria, were not immediately re-tested with smaller doses but who when re-tested later gave a positive reaction to 0.01 milligram or less. It is worthy of note that all clinic patients who have given vesiculated reactions to 1.0 and to 0.1 milligram when re-tested at a later date have given a positive reaction to 0.01 milligram or less.

It is important to emphasize the fact that the patients here studied are classified according to the maximum degree of hypersensitivity demonstrated before their third birthday. In order to be certain that no patient included in either Group I or Group II was in the early stage of his disease, before his maximum level of hypersensitivity had been reached, it was demanded that he show no increase in allergy when retested with the same and smaller doses of tuberculin one year or more after the initial positive test.

Of the 186 children surviving only eight were followed for as short a period as two years. The maximum period of follow-up was seventeen years. The mean period was nine years for Group I, five years for Group II, and seven years for Group III.

In each group there was a predominance of negro children. In Group I there were twenty-seven negro as compared to seven white; in Group II nineteen negro and seven white; in Group III one hundred and fourteen negro and thirty-five white. There were five more males than females in the whole group studied.

RESULTS

Two hundred and seven children presenting a positive reaction to tuberculin before their third birthday are included in the present study. Thirty-four were positive only to the 1.0 milligram dose of tuberculin, twenty six to the 0.1 milligram dose, and one hundred and forty-seven to the 0.01 milligram dose or the equivalent described.

When these children were retested with tuberculin in the three doses described through the subsequent periods of observation it was ap-

parent that each group showed marked differences in the persistence and degree of hypersensitivity. Thirty (88%) of the thirty-four children positive only to 1.0 milligram showed loss of hypersensitivity on subsequent retest: twelve were insensitive when retested one year after their first positive reaction to 1.0 milligram; the others were either not immediately tested or became negative at a later stage in their disease. Nine of the thirty subsequently redeveloped hypersensitivity; nineteen followed for an average period of four years did not; two have not as yet been retested.

Eleven (42%) of the children who reacted to a minimum of 0.1 milligram were negative to that dose on a subsequent retest. Of the eleven, five were negative to 0.1 milligram when retested one year after the first positive reaction to 0.1 milligram. Four of these children have remained insensitive to that dose. Of the eleven who showed a reduction in sensitivity, five were again positive to 0.1 milligram when retested, two remained negative to the 0.1 milligram dose but were positive to the 1.0 milligram dose, and four became unresponsive even to the 1.0 dose. Thus six, or (23%) showed a persisting loss of hypersensitivity to 0.1 milligram which so far has lasted an average of four and one half years.

One hundred and two, of the one hundred and forty seven children reacting positively to the 0.01 milligram, or the equivalent mentioned, were retested with 0.01 milligram of tuberculin. Only ten of this group showed any reduction of sensitivity, two have not yet been retested, and in eight this was only temporary, as they gave positive reactions to subsequent tests with 0.01 milligram doses; five were positive when retested the succeeding year; three were not retested for some time but were positive to 0.01 milligram when retested after two years, three years and five years respectively. The period of time between the initial positive reaction to 0.01 milligram and any reduction in sensitivity varied between two and eleven years with an average of 4.8 years. Five of the individuals who became temporarily insensitive to the 0.01 dose remained senstive to the 0.1 dose, one was tested only with the 1.0 dose and found to be sensitive at that level, the other four were not immediately tested with larger doses.

This difference in the persistence of the positive tuberculin test cannot be attributed to the time factor alone as the median period of

observation of the children who showed persistence of the positive tests was longer than the median period required for the test to become negative in the groups in which this occurred. In the succeeding paragraphs, it will be seen that the degree of hypersensitivity was definitely related to the extent of detectable tuberculous lesions.

Pulmonary and Mediastinal Lesions as Demonstrated by X-ray: The roentgen-ray findings have been grouped according to the presence or absence of non-calcified parenchymal lesions considered to be tuberculous in origin, and of intrathoracic calcification. The parenchymal lesions comprise only those of a rather extensive nature as no attempt has been made to classify mediastinal lymph node involvement even when obvious, as it is often extremely difficult to determine with accuracy the presence of mild mediastinal lesions. It is significant however, that although an occasional child who reacted only to the 1.0 milligram dose of tuberculin showed mild root changes compatible with, but not diagnostic of, mild mediastinal tuberculosis, a large number of the children who reacted to the 0.01 milligram dose showed extremely severe involvement of the mediastinal nodes and indeed in the majority of cases went on to deposit calcium in these diseased areas. No distinction is made between calcified lesions occurring in the lung parenchyma and the mediastinal glands, as this is frequently not possible. Many patients deposited calcium in both sites. As seen in the accompanying table, none of the children positive only to the 1.0 milligram dose of tuberculin developed detectable parenchymal lesions or intrathoracic calcification. In the group reacting to the 0.1 dose one child showed a parenchymal lesion, and three developed calcification. However, in the highly sensitive group of those reacting to 0.01 milligram, 43 per cent showed frank parenchymal lesions and 62 per cent developed intrathoracic calcification; and of those giving vesiculated reactions to 0.1 milligram, 50 per cent showed parenchymal lesions and 77 per cent developed intrathoracic calcification.

Extrapulmonary Tuberculosis: In like manner, when other manifestations of tuberculous infection were considered, none was found to be present in the group reacting to the 1.0 milligram test dose. In the group reacting to the 0.1 milligram dose one child developed phlyctenular keratitis, and another tuberculosis of the bones. In the group positive to 0.01 milligram of tuberculin, twenty-six (25%) of

the children had extrapulmonary manifestations of tuberculosis, and fourteen (14%) of these children died of the disease. In the other highly sensitive group (those giving vesiculated reactions to 0.1 milligram), twelve (27%) had evidence of extrapulmonary tuberculosis; seven (16%) died. The extrapulmonary manifestations of tuberculosis for the whole group of one hundred and forty seven highly sensitive children consisted in meningitis in twelve instances, miliary tuberculosis in nine, involvement of the bones or joints in ten, tuberculosis of the skin in eight, phlyctenular keratitis in ten, tuberculous empyaema in three, cervical adenitis in three, tuberculous otitis media in three, and renal tuberculosis in one instance. A number of children showed more than one such manifestation.

TABLE I

MINIMUM DOSE OF TUBERCULIN GIVING POSITIVE REACTION	TOTAL NUMBER OF PATIENTS IN EACH GROUP	NUMBER RETESTED TO MINIMUM DOSE	NEGATIVE AT A SUBSEQUENT TEST TO DOSE PREVIOUSLY POSITIVE		REMAINING NEGATIVE TO MINIMUM DOSE PREVIOUSLY POSITIVE		ROENTGEN RAY FINDINGS IN INITIAL OR SUBSEQUENT FILMS OF CHEST				EXTRA-PULMONARY MANIFESTATIONS OF TUBERCULOSIS				DEATHS	
							Non calcified parenchymal lesions		Intrathoracic calcification		Associated with positive pulmonary roentgen findings		In absence of positive roentgen findings in chest			
			Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1.0 mgms.	34	34	30	88	19*	56*	0	0	0	0	0	0	0	0	0	0
0.1 mgms.	26	26	11	42.3	6	23	1	2.6	3	7.8	2	5.2	0	0	0	0
0.1 mgms. (vesiculated)	44	37	0	0	0	0	22	50	34	77.2	12†	27.2	0	0	7	15.9
0.01 mgms.	103	65	10	15	?0*	?0*	44	42.7	64	62.1	26‡	25.2	4	3.8	14	13.6

* Two were not retested.
† 9 parenchymal, 3 calcification only.
‡ 21 parenchymal, 5 calcification only.

In the whole group of one hundred and forty seven children, seventeen showed no evidence of tuberculosis apart from a high degree of sensitivity to tuberculin.

SUMMARY

1. A group of two hundred and seven children, infected with tuberculosis has been studied and classified on a basis of the degree of

sensitivity to old tuberculin, given intradermally, before their third birthday.

2. Thirty-four reacted to not less than 1.0 milligram of tuberculin. Nineteen (56%) of these subsequently lost their hypersensitivity and did not regain it during the period of study. None of these thirty-four children showed demonstrable parenchymal lesions or calcification on x-ray of the chest; none developed extra-pulmonary tuberculosis, and none died.

3. Twenty-six reacted to 0.1 milligram of tuberculin. Six (23%) of these subsequently lost their sensitivity to this dose and did not regain it. Only one of the twenty-six had parenchymal involvement and three showed subsequent calcification on x-ray of the chest. Two had extrapulmonary tuberculous manifestations of the disease; none died.

4. In the highly sensitive group, one hundred and three children reacted positively to the 0.01 milligram dose and forty-four gave vesiculated reactions to 0.1 milligram. Of those positive to 0.01 milligram, 43 per cent had non-calcified parenchymal lesions, 62 per cent of the one hundred and three developed intrathoracic calcifications, 25 per cent had manifestations of extrapulmonary tuberculosis, 14 per cent died, 12 per cent had no evidence of tuberculosis apart from a positive tuberculin test. Of the forty-four giving vesiculated reactions to 0.1 milligram, 50 per cent had parenchymal lesions, 77 per cent developed intrathoracic calcifications; 27 per cent had extrapulmonary manifestations of the disease, 16 per cent died, 12 per cent had no evidence of tuberculosis except for a high degree of sensitivity to tuberculin.

5. No child in the markedly hypersensitive group sustained a persistent loss of sensitivity to the 0.01 milligram dose of tuberulin.

CONCLUSIONS

In this study the prognosis for children under three years reacting positively to not less than 1.0 or 0.1 milligram of tuberculin (except in overwhelming disease or in a very early stage of the infection) was good, in sharp contrast to those children who were highly sensitive where the prognosis was bad. The degree of hypersensitivity was closely related to the extent of the tuberculous lesions.

Those children who developed only a low degree of sensitivity to tuberculin showed a marked tendency to lose their reactivity, while those who developed a marked sensitivity, tended to remain hypersensitive. The tendency to lose hypersensitivity was likewise related to the extent of the tuberculous lesions.

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STUDIES ON ACUTE SCHISTOSOMIASIS JAPONICA IN THE PHILIPPINE ISLANDS

I. A Clinical Study of 337 Cases with a Preliminary Report on the Results of Treatment with Fuadin in 110 Cases

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I. INTRODUCTION

The reoccupation of the island of Leyte began on 20 October 1944 The general hospital in which these studies were made arrived in mid-November and began to receive patients on 4 December. By the latter part of December cases of schistosomiasis japonica began to enter the hospital. A considerable number of such patients passed through this hospital in succeeding months.

In retrospect, it is apparent that most of the patients contracted the disease during the early weeks of the military operation when exposure to waters subsequently proven to be infested with the cerceriae of *Schistosoma japonicum* was unavoidable in many instances. For example, cases appeared among engineers building bridges over infested streams, among combat troops who came into contact with swamps and streams, and among service troops who washed vehicles and clothing in streams and rivers. Personnel of certain units bathed or swam in rivers before showers or bathing facilities were established.

As active military operations diminished in late January, it became possible to establish measures effective in preventing further contact with infested waters, and, as a consequence, practically all exposures ceased except in troops still engaged in combat. This accounts for the fact that the vast majority of patients with schistosomiasis who were subsequently hospitalized gave a history of exposure during November and December, 1944. A number of cases diagnosed as

late as April 1945 were picked up only as the result of surveys. These patients gave a history of exposure only during November and December 1944.

Leyte is one, if not the chief, source of schistosomiasis in the Philippine Archipelago. Garrison[1] in 1908, according to Africa and Garcia[2], was the first to report on human infection with the blood fluke, *Schistosoma japonicum*, on Leyte. In 1941, surveys in the Philippine Islands made by Tubangui and Pasco[3] revealed four islands whereon the disease was endemic: Leyte, Mindoro, Mindanao and Samar. Human cases were limited to the eastern side of Leyte and Mindoro, to the northern tip of Mindanao, but were more widely distributed on Samar which is immediately to the northeast of Leyte. Their observations indicated that approximately 20 per cent of the populace was infected. Surveys made during the past four months by Army Malaria Survey and Research Units[4] indicate in endemic areas on Leyte an even higher rate. On the basis of only one stool examination per individual, the incidence of infection ranged from 10 per cent in infants to 80 per cent in adolescents 11 to 15 years old. It was somewhat lower, 67 per cent, in individuals of 16 years or over. The rate was generally higher in males.

Clinical studies on schistosomiasis japonica have dealt principally with patients in the chronic stage of the disease. A few cases observed at onset have been described by Faust and Meleney[5] (1924), by Kastein[6] (1932), and by Egan[7] (1936). An opportunity to study the early phases of the disease in a large group of previously unexposed individuals was never afforded prior to the present military operation.

A brief description of the life cycle of the parasite, *Schistosoma japonicum*, follows. Standard textbooks on tropical diseases should be consulted for complete elucidation of the subject. The ova of the worm appear in stools of such infected animal hosts as man, dogs, cats, rats, mice, and, in this area, water buffalo, which, deposited on the ground, are washed by surface water into swamps or streams. Within 6 to 36 hours, the shells of the ova break, releasing free-swimming miracidia into the water. To continue the cycle, the miracidia must find a suitable snail host (in the Philippine Islands, a small fresh water snail, *Oncomelani quadrasi* or *Oncomelani hydrobiopsis*) or die within approximately 24 hours. If a suitable snail is found,

the miracidia attach themselves, penetrate, and eventually reach the liver. Here the miracidia enlarge into saclike structures, the first generation sporocysts, which give rise to a second generation of sporocysts; these in turn produce the fork-tailed cerceriae. This cycle takes from 5 to 7 weeks. The cerceriae emerge irregularly from the snail as free-swimming larvae, which, in order to survive, must find a suitable mammalian host within 36 hours. Faust and Hoffman[8] estimated from studies on *S. mansoni* that a snail infected with only one miracidium might release, over a period of time, as many as 100,000 to 250,000 cerceriae. This figure is much lower when snails are infected with miracidia of *S. japonicum*. Studies indicate that the individual snail is usually infected with larvae of only one sex. For the development of the disease in mammals it is necessary that cerceriae of both sexes, as yet undifferentiated at this stage, enter the host. The cerceriae attach themselves to the host by means of ventral suckers, lose their tails, and rapidly penetrate the unbroken skin. At this time, the latent period of the disease begins. The cerceriae, now known as schistosomulae, enter the lymphatic and blood vessels, circulate through the body, and lodge principally in the liver and mesenteric veins. Over a period of from 2 to 10 weeks they develop, reach maturity, and migrate principally to the small veins and venules of the mesenteric vessels. Here mating occurs and ovulation begins. The ova may erode through the vessel walls into the tissues and thence through the intestinal mucosa into the lumen of the bowel; or they may be swept by the portal circulation to the liver. Some of the ova, however, reach the systemic circulation and may lodge in the lungs and other organs.

II. CLINICAL CASES AND DATA TO BE PRESENTED

In this hospital the diagnosis of schistosomiasis japonica has been made on 337 cases in the four-month period from late December 1944 to the end of April 1945. For the general discussion, reference will be made to the entire series, but the charts and tables are based on the first 75 consecutive cases which have been subjected to detailed analysis.

The material to be presented includes observations on exposure, epidemiology, latent period, symptomatology and physical findings,

blood examinations, a special modification of the sedimentation method to demonstrate ova in stools, the clinical response to treatment, and a brief summary of post-treatment results so far available in 110 cases.

III. EXPOSURE

All of the 337 cases of schistosomiasis acquired the disease on Leyte island. The manner of exposure or contact with fresh water has been outlined above. Exposure or contact with fresh water varied considerably from only one to repeated contacts, covering a period of minutes, hours, or even several days or weeks. Twelve patients were in contact with infested water for a few minutes to several hours on one day only. Of these, 7 went swimming for a period of approximately 30 minutes; 3 waded in the water for several hours while building bridges; and 2 merely washed their hands and arms in a stream. A rough approximation of the duration of exposure is given in Table I.

Not all individuals, however, who were in contact with fresh water in endemic areas developed the disease; at least, so far as our present information indicates. In this regard, we have had the opportunity to survey one particular military unit, of which 164 admitted swimming or bathing in a river now known to be infested. Of these, 67 developed symptoms and the disease was proven to be present by demonstration of ova in the stools. A routine survey of the remaining individuals brought to light 8 more cases in which the disease was asymptomatic. Thus, 75 or 45 per cent of individuals exposed in this particular unit developed the disease. This incidence is slightly lower than that found by Egan[7], who reported that 12 of 18 men of the British Navy stationed in China developed schistosomiasis after swimming. Why, under similar conditions of exposure, one individual contracts the disease and another does not, is not clear. From the standpoint of prevention of the disease, however, it is of the utmost importance to realize that very brief contact with infested water alone is sufficient to permit the cerceriae to attach themselves to the skin.

Itching of the skin, frequently described[9] as due to penetration of the skin by cerceriae, was uncommon in this series. A history of itching soon after exposure was given in only 9 of the 75 cases analyzed

in detail. It was referred to as a feeling of red ants or a burning sensation which developed about 30 minutes after contact with fresh water and lasted for an hour or more. Skin eruptions, such as that

TABLE I

Latent Period in 73 Cases

Latent period could be accurately estimated in 12 cases (first column) as exposure was limited to only one day. In the remaining cases, exact latent period could not be calculated accurately as exposure varied as indicated. The latent period in these cases was estimated from the first day of exposure. It should be noted that the average latent period in cases exposed up to 14 days is relatively uniform. In 2 cases, latent period could not be determined.

	DURATION OF EXPOSURE				
	1 day	2-7 days	8-14 days	15-21 days	22 or more days
	12 cases	13 cases	16 cases	15 cases	17 cases
Latent period in days in 73 cases	26	30	34	26	26
	26	26	25	31	28
	33	27	27	32	37
	37	30	27	34	39
	37	30	28	40	40
	44	35	32	44	40
	46	36	32	45	40
	46	37	52	51	42
	48	42	41	53	46
	50	47	42	54	46
	55	53	43	55	48
	58	53	46	60	55
		54	46	61	55
			47	73	57
			52	78	59
			61		60
					61
Minimum.....	26 days	26 days	25 days	26 days	26 days
Maximum.....	58 days	54 days	61 days	78 days	61 days
Average.....	42 days	46 days	39 days	52 days	46 days

noted by Egan[7] in one of his patients, were not observed by any of our patients and none were reported by medical officers of units from which the patients in this group were derived.

IV. LATENT PERIOD

This is defined as the period of time elapsing from initial exposure to water infested by cerceriae to the onset of symptoms. Data on this period are limited since few cases were observed at the onset of symptoms. In Egan's[7] series of 12 cases in China, the latent period varied from 5 to 6½ weeks; in Kastein's[6] 15 cases, from 4 to 6 weeks; and in the case described by Faust and Meleney[5], it was 26 or 27 days. Our data show considerable variation, even in individuals exposed to infested water on only one occasion, as is seen in Table I.

In 12 cases, the exact and only day on which the individual was exposed is known; the shortest latent period in this group was 26 days, the longest 58 and the average 42.

In the remaining cases, the latent period could not be so accurately estimated as exposure varied from several days to several weeks, and penetration of the skin by cerceriae could have occurred on any one or all of the days on which the individual was in contact with fresh water. The latent period in these cases was estimated from the first day of exposure. Even when contact with infested water covered a period up to 14 days, the latent period, according to our calculation, was fairly uniform as shown in Table I. As duration of exposure increased, however, there was apparent lengthening of the latent period, although the data could be interpreted as indicating that infection did not take place on initial contact, but only after several exposures.

Further analysis indicates that the latent period in cases presenting the more severe symptoms was usually, but not always, shorter than in the cases with mild symptoms. In 45 patients presenting severe (4) or moderately severe (41) symptoms, the shortest latent period was 28 days, the longest 60 days, and the average 41 days. In patients with mild symptoms, the shortest period was 26 days, the longest 79 days, and the average 50 days.

It is difficult to correlate the course of the disease, including the latent period, onset of the symptoms, and the demonstration of ova in the stool, with the life cycle of the parasite. Fourteen patients, in whom the latent period varied from 41 days to 79 days, became available for study soon after the onset of symptoms. Ova were quickly demonstrated in the stools: as early as the seventh day after the

onset of the symptoms in one patient, and in the remaining 13 cases from the eighth to the fifteenth day, as shown in Table II. Ova

TABLE II

Onset of Symptoms Correlated with Appearance of Ova in Stools

In 14 cases studied early after onset of symptoms, the latent period and the day on which ova were demonstrated are tabulated. Data illustrate that ova of schistosomiasis japonicum are found soon after onset of symptoms, indicating that initial symptoms are correlated with the completion of maturation of the worm, or with the deposition and dissemination of ova, or with both these factors.

CASE NO.	LATENT PERIOD (TIME FROM FIRST EXPOSURE TO ONSET OF SYMPTOMS)	DAYS FOLLOWING ONSET OF SYMPTOMS WHEN OVA WERE DEMONSTRATED
10	42 days	10th day (1st stool examined)
11	50 days	12th day (Stool negative on 8th day)
13	48 days	14th day (Stool negative on 13th day)
20	52 days	8th day (Stool negative on 6th day)
33	79 days	10th day (Stool negative on 9th day)
36	55 days	12th day (Stool negative on 6th, 8th and 9th days)
39	46 days	13th day (1st stool examined)
47	51 days	13th day (1st stool examined)
48	59 days	10th day (1st stool examined)
63	53 days	10th day (1st stool examined)
66	52 days	7th day (1st stool examined)
67	41 days	12th day (1st stool examined)
70	47 days	15th day (Stool negative on 13th day)
72	51 days	12th day (Daily stools from 7 to 11 days inc. negative)

were likewise demonstrated soon after onset of symptoms in Egan's series, although the exact day is not recorded. These data suggest that the onset of symptoms of schistosomiasis japonica is closely re-

lated either to the completion of maturation of the worm, or to the deposition and dissemination of the ova, or to both of these factors. On the other hand, the period between the onset of symptoms and the demonstration of ova in the stool may be much longer than in the 14 patients cited. This may be accounted for by the supposition that it may take ova, once deposited, varying periods of time to reach the lumen of the intestine. Many ova never reach the intestinal lumen. Finally, although ova may be present in a patient's stool, their demonstration may require many time-consuming examinations.

V. MODE OF ONSET, CLINICAL SYMPTOMS, AND COURSE OF DISEASE

The onset of symptoms was usually more or less abrupt with headache, chills, feverishness, cough, urticaria, generalized aches, and anorexia of varying severity. In some cases, the onset was insidious and the symptoms, thereafter, somtimes were mild (even throughout the symptomatic phase) or, after several days, they were sometimes abruptly intensified. In a few instances, the onset was not only abrupt, but also severe or fulminating in character. Lastly, the disease sometimes had an asymptomatic course; such cases were detected through group surveys. On the basis of intensity and severity of symptoms and the height and duration of fever, the series of 337 cases has been divided into four groups, as follows: *severe*, 21 cases; *moderately severe*, 123 cases; *mild*, 168 cases; and *asymptomatic*, 25 cases. The incidence of the chief symptoms as shown in Table III, however, is based on the 75 cases subjected to detailed analysis. It should be stated that this classification is based on clinical grounds only, and does not imply that the severity of symptoms is necessarily correlated with the degree of infection.

Moderately severe group. The symptoms usually began suddenly with fever, chills, headache, generalized aches and pains, soreness and stiffness of the neck, upper abdominal discomfort accompanied by anorexia, urticaria, and an irritating dry hacking cough, all or part of which lasted from two to eight weeks. Chart 1, Case 45 and Chart 2, Case 4, represent examples of this type.

In 14 cases, 8 of which presented the shorter latent periods, the acute febrile illness considered as ushering in the symptomatic phase of the disease partially or entirely subsided in from 2 to 8 days; there-

after, the symptoms persisted in mild form, or remained completely in abeyance for a week or two, when gradual or sharp accentuation of symptoms developed. This initial acute illness, somtimes clearly demarcated, and separate from, and sometimes apparently merging with, the definitive symptoms, suggested dengue, currently endemic at the time in this area. Typical skin eruptions of dengue were

TABLE III

Incidence of Symptoms in 75 Cases of Schistosomiasis Japonica

SYMPTOMS	INCIDENCE	PERCENTAGE OCCURRENCE OF EACH SYMPTOM
	patients	
Fever	75	100
Headache	69	92
Weight loss	69	92
Malaise	67	89.3
Anorexia	66	88
Upper abdominal pain	60	80
Stiff neck	57	67
Abdominal cramps	52	65
Cough	48	64
General aches, Backaches, Arthralgia	45	60
Urticaria, Angioneurotic edema	39	52
Chills	37	49
Diarrhea	21	28
Constipation	18	24
Chest pain	17	22
Itching (after exposure to infested water)	9	12
Testicular aching	9	12
Neurological	7	9.3
Nausea and vomiting	6	8
Asthma	6	8

never noted, however, and we believe this acute febrile period is part of the early symptomatic phase of schistosomiasis, and represents the host reaction to the initial dissemination of ova.

At first, the chief complaints in many cases were fever, chills, headache, cough, urticaria and/or angioneurotic edema; in several cases, the first manifestations were limited to lesions in the skin. Later,

within a few days to 2 weeks, the urticaria and cough in most cases subsided but the upper abdominal pain or discomfort, the anorexia, loss of weight, headache, evening fatigability, stiff-neck, and varied myalgic and arthralgic pains persisted, though fluctuating from day to day.

The febrile stage lasted from 1 to 8 weeks; the fever was remittent and of the saw-tooth type; it rose sharply to 102 to 104 degrees in the evening and, with rare exceptions, returned to normal or below normal in the morning. Likewise, there was diurnal variation in the intensity of symptoms; the majority of the patients felt better or "tolerably" well in the morning, but worse in the afternoon and evening, when all symptoms were characteristically intensified.

Urticaria or angioneurotic edema, which was noted in 52 per cent of cases, varied from an occasional small and fleeting wheal to lesions of tremendous size. The lesions were indolent and persistent. They were not strikingly responsive to adrenalin. Swelling of the posterior half of the tongue was noted in one patient, but edema of the fauces and larynx was not seen.

A very common and noteworthy symptom, not heretofore referred to, was soreness and stiffness of the neck. Egan[7] mentions, however, "signs of meningeal irritation" in one of his 12 patients. Fifty-seven patients of this series complained of this symptom and in some it was striking. Usually it developed suddenly and lasted from 24 to 48 hours, then subsided, only to recur again in several days' time. In one patient, the neck was held rigid and stiff, defying any movement for a period of 2 weeks. Lateral rotation was especially restricted and, less commonly, flexion. This complaint is probably not meningeal, but more likely myalgic in origin, as soreness of the trapezius and sterno-cleido-mastoid muscles was elicited on palpation. Meningitis was suspected, but spinal fluid examinations revealed no abnormalities.

In association with anorexia and upper abdominal discomfort, abdominal cramps were frequent, but diarrhea, described by previous authors in the stage in which ova are found in the stools, occurred in only 21 cases (28 per cent), and then it was not clear whether it was a part of the disease or due to intercurrent infection, as attacks of diarrhea were frequent in many units in this area. More frequently, the bowel movements were normal or constipation, sometimes severe

as the disease progressed, was present. Blood was rarely found in the stools and when found was demonstrated only in the occult form. Anorexia and loss of weight, which in long-standing cases may amount to as much as 25 pounds, were prominent.

A non-productive cough was sometimes accompanied by moist rales or scattered areas of consolidation, especially at the lung bases; or by diffuse signs characteristic of acute asthmatic bronchitis which occasionally at first dominated the clinical picture. In cases of the latter type, the true nature of the disease was not suspected in some instances until more characteristic symptoms appeared.

Alopecia, which has been noted by Hunt[10] in several of a series of 18 patients who contracted the disease on the adjacent island, Samar, was not seen in this series. Lesions of the skin containing nests of ova, reported in one case from this area by Garcia, Navorro and Bautista[11], were not observed.

Mild group. The symptoms and physical findings in this form of the disease were often minimal. In many cases, patients complained toward evening of occasional cough, slight feverishness, malaise, headache, fatigability, and anorexia. Occasionally they had mild upper abdominal discomfort, transitory scattered aches and pains, and at times they complained of a "crick" in the neck. They did not seek medical attention for days or even weeks, but attributed their symptoms merely to the unaccustomed tropical environment. When a patient reported to sick call in the morning, as a rule his temperature was normal and he felt well so that the infection was easily over-looked. In fact, such vague and variable symptoms led to the diagnosis of psychoneurosis in several individuals before schistosomiasis was discovered.

Physical examination in many cases of this type revealed weight loss, enlargement of the posterior cervical lymph nodes, tenderness in the epigastrium and right upper quadrant of the abdomen and a slightly enlarged liver. The spleen was seldom palpable. Chart 3, case 66, illustrates such a mild case with a short episode of low grade fever and minimal abnormal physical findings.

Severe group. In 7 patients the symptoms previously described were sufficiently severe to justify this classification. Chart 1, case 45, illustrates this group. The patients were often prostrated and

semi-comatose, the fever was high and spiking, and the headaches, generalized aches and pains, cough and anorexia were in accord. Enlargement and tenderness of the liver were more pronounced and the spleen was uniformly enlarged. In a few patients in this series, mild anemia was observed. Several of the severe cases had neurological manifestations which will be described below (Section VI).

Asymptomatic group. In 25 cases of the complete series, the disease developed without symptoms; no such cases occurred among the 75 studied in detail. Schistosomiasis was suspected in these cases because of known exposure to infested water, or because of the discovery of eosinophilia, either during a routine survey of military units in

TABLE IV

Incidence of Important Physical Findings, in 75 Cases of Schistosomiasis Japonica

PHYSICAL FINDINGS	INCIDENCE	PERCENTAGE OCCURRENCE OF EACH PHYSICAL FINDING
	patients	
Liver (Enlargement or tenderness)	69	92
Epigastric tenderness	63	84
Enlargement of spleen	51	67
Enlargement of posterior cervical lymph nodes	27	36
General enlargement of lymph nodes	25	33
Objective pulmonary changes	5	6
Objective neurological changes	3	4

which other members were known to have schistosomiasis or during hospitalization for another disease. The incidence of this type of disease among troops who were stationed in endemic areas is impossible to estimate and could only be determined by extensive surveys of such units.

VI. PHYSICAL FINDINGS

Table IV presents a list of the most frequent physical findings. Patients with schistosomiasis japonica of moderate severity usually appeared thin, the degree depending, however, on the duration of symptoms. They look sallow and chronically rather than acutely ill. In the absence of urticaria, the skin was normal. Enlargement of the posterior cervical lymph nodes, and less often a mild general

enlargement of all the lymph nodes, was found. The mucous membranes in some cases were pale. The eyes, ears, nose, mouth, and throat were normal. Since cough was a frequent complaint, one might have expected frequent changes in the lungs, but in most cases abnormal pulmonary signs were not elicited. Only 5 patients in this series had objective pulmonary changes. These were scattered areas of infiltration demonstrable by x-ray. In two cases seen more recently, signs of consolidation at one base were found. In most instances, the abnormal findings were of short duration, a matter of one or two weeks, after which they disappeared. In one severe case observed at another hospital, typical miliary seeding (pseudo-tubercles of the lungs) similar to that described in schistosomiasis mansoni was found. The cause of the x-ray changes is not definitely known, but they are probably due to deposition of ova in the peri-bronchial tissues as has been demonstrated post-morten in the *S. mansoni* type, and as has been found in one fatal case in this area. Sigmoidoscopic examination in some instances revealed pseudo-tubercles, or small nodules, on the mucosal surface of the intestine. These nodules are slightly yellowish in color, about 2 mm. in diameter, and contain both mature and immature ova, as described by Johnson and Berry[12] in a series of cases from this area.

The heart and blood pressure were normal; the pulse rate varied in direct relationship to the temperature. The abdomen was usually flat but occasionally somewhat distended. There was often mild generalized tenderness, usually limited to the upper abdomen, and especially to the mid-epigastrium where tenderness to palpation and percussion were often exquisite. The liver was tender and palpably enlarged in 69 patients (92 per cent) of our special group. It extended as much as 6 cm. below the costal margin in some instances, but in many cases the enlargement was demonstrable only by widening of the area of dullness. Even in the latter cases, there was tenderness to deep palpation below the right costal margin and to percussion over the liver area. The spleen was enlarged in 67 per cent of the 75 cases. It may extend as much as 4 cm. below the costal margin, but in a few instances enlargement was indicated only by increased dullness over the splenic area. The spleen was slightly or not at all tender. Although testicular pain was complained of by several patients, the genitalia were normal.

The neurologic symptoms and signs shown by 7 patients in this series are of great interest. Two patients exhibited severe manifestations of extensive involvement of the central nervous system, which developed concurrently with the usual symptoms, but, thereafter, dominated the clinical picture. In Chart 4, case 51, whose record is given in detail below, cerebral manifestations were especially prominent, and appeared in the following sequence: Apathy, disorientation, coma, clonic spasms of upper and lower extremities with flexion of the arms and extension of the legs, incontinence of urine and feces and evidence of involvement of the pyramidal tracts with hyperreflexia, bilaterally positive Babinski responses and clonus. A third patient noted rapidly progressive weakness of his left arm and 5 days after the onset of fever, neurological examination revealed typical left hemiplegia with hyperactive deep reflexes, positive Hoffman and Babinski signs and increased muscle tonus. There was mild weakness of the right arm and leg, with hyperactive reflexes and evidence of pyramidal tract involvement. Involvement of the central nervous system was described in 1941 by Vitug, Cruz and Bautista[13] who reported 2 cases from this area and refer to two other cases. Egan[7] also commented on the cerebral symptoms and neurologic abnormalities occuring in 2 of his 12 cases, and the description of his case 5 is very similar to our case 51.

Paraesthesia and numbness of the extremities were complained of by two patients. In one patient, symptoms were limited to the distribution of both ulnar nerves, without objective sensory changes. An additional patient gave a history of transient impairment of vision in the left temporal field, but on examination by an ophthalmologist, no abnormality could be found. The last patient in the group, shortly after the onset of his symptoms, developed peripheral peroneal nerve palsy with foot drop, but since such lesions have developed independently or have been noted in association with other diseases, one cannot definitely attribute this lesion to schistosomiasis.

VII. LABORATORY DATA

Significant laboratory findings were limited to the characteristic eosinophilia and to ova of *Schistosoma japonicum* in the stools.

Leucocytosis and eosinophilia. In most instances there is an in-

crease of white blood cell count. Usually the total leucocytes varied from 9,000 to 30,000, of which the eosinophiles comprised from 6 to 95 per cent. The highest white cell count found was 53,000, 83 per cent of which were eosinophilic leucocytes. An increase of the eosinophilic leucocytes of blood is one of the characteristic features of the disease and few diseases produce such marked eosinophilia. In every case of the 75 analyzed in detail, the total eosinophile count was elevated, varying from 500 to 48,990 cells.

No relationship between the severity of clinical symptoms and the degree of eosinophilia was found. Table V presents data in support of this observation. It will be noted that the increase of eosinophiles was essentially the same in the severe, moderately severe, and mild cases. There was a tendency for the eosinophilic leucocytes to increase as the disease progressed, and, occasionally, after reaching a

TABLE V

Demonstrates that There is No Correlation between Severity of Symptoms and Eosinophilia

EOSINOPHILES (TOTAL NUMBER)	MILD	MODERATELY SEVERE	SEVERE
500–5,000	14 cases	16 cases	2 cases
5,000–20,000	15 cases	16 cases	4 cases
20,000 or above	2 cases	4 cases	1 case

maximum number, they remained stabilized at this level for several weeks. On the other hand, it was more commonly found that the total number fluctuated from week to week without relationship to the clinical symptoms. There were also a few patients in whom the eosinophiles were only slightly increased, and this slight elevation sometimes persisted well into, and occasionally throughout, the course of active symptoms. A further point of considerable diagnostic significance was noted, namely that in several mild and asymptomatic cases (not included among the 75), the eosinophiles were within normal limits, and did not increase in number throughout the period of observation. In general, however, no consistent trend in the eosinophilia was noted during and immediately after treatment although symptoms had subsided and the temperature had become normal. In 33 cases, the general level was unchanged, in 34 there was definite decrease, while in 7 an increase was found, as indicated in Table VI.

Anemia was noted during the course of the disease in only 6 cases, 3 in the moderately severe, and 3 in the severe group. The erythrocyte count was not lower than 4,000,000 per cmm., with 13 gms. of hemoglobin. In one case, however, the red cells dropped to 2,800,000 with a hemoglobin of 8 gms. This patient, however, also had a moderately severe hookworm infection.

In patients with neurological manifestations, spinal fluid examinations were normal.

Stool examinations. Diagnostic or pre-treatment stool examinations in the 75 cases analyzed in detail showed mature viable ova in 71 instances and immature ova in 4 instances. Of the latter, mature ova were eventually found in one patient. Many cases required 2 or more stool examinations before ova were found. In 20 patients,

TABLE VI

Trend of the Eosinophilia During and After Treatment

During period of observation, the general level of eosinophiles did not change in 33 cases; in 34 a definite decrease was found and in 7 a definite increase.

TOTAL NUMBER EOSINOPHILES	NO CHANGE	DECREASE	INCREASE
500–5,000	19 cases	8 cases	5 cases
5,000–20,000	14 cases	19 cases	2 cases
20,000 or above	0 cases	7 cases	0 cases
Total number of cases...	33 cases	34 cases	7 cases

ova were found on the first examination, and 26 were positive on the second examination. The 29 remaining cases became positive on the third to the eighth examination. Most of the cases requiring 5 or more stool examinations were of the mild type clinically. The week of the disease in which stools were positive is given in Table VII, together with the duration of fever and symptoms prior to therapy (therapy was begun as soon as ova were found). In general, stool examinations were not repeated during the course of treatment as laboratory facilities available at the time were limited and were fully engaged in examining new cases. Stool examinations in 24 cases remaining under observation after treatment was completed and is summarized in Section VIII; the remaining 51 cases were evacuated immediately or very soon after treatment was completed.

Other parasitic ova found included those of hookworm in 8 patients, *Strongyloides* in 1, cysts and trophozoites of *Endamoeba histolytica* in 4, *T. hominis* in 2, and hookworm and trophozoites of *E. histolytica* combined in 1.

After experimentation with several methods, the following procedure has been employed to find schistosome ova in stools. A fecal sample (about half the size of one's thumb, 7 to 10 gms.) is taken for emulsification. Mucus particles are more likely to contain ova, but if no mucus

TABLE VII

Duration of fever (and symptoms) prior to treatment in 72 patients is compared to duration of fever following institution of therapy. Data indicates that regardless of duration of fever (and symptoms) prior to treatment, response to therapy as measured by fever is quite uniform. In 63 patients, temperature reached normal within 28 days after treatment was started; in 7 symptomatically improved, temperature remained slightly elevated while under observation; in 2 no improvement was noted. 3 patients, not tabulated, had become afebrile prior to treatment.

DURATION FEVER PRIOR TO THERAPY	NUMBER OF PATIENTS	DURATION OF FEVER AFTER INSTITUTION OF THERAPY			MILD IMPROVEMENT	NO IMPROVEMENT
		Days				
		7–14	15–21	22–28		
7–14 days	6	1	3	2		
15–21 days	11	2	7	1	1	
22–28 days	12		7	4		1
29–35 days	17	3	8	2	4	
36–42 days	12	2	7	1	1	1
43–49 days	10	2	6	1	1	
50–56 days	1	1				
57–63 days	1	1				
64–70 days	2	1	1			
Total patients	72	13	39	11	7	2

is present the sample is selected at random from several areas, preferably from the surface of the stool. The specimen is placed in a beaker, moistened with tap water and broken up with a spatula until a pasty mass is formed. Addition of water and mixing throughly emulsifies the sample for the next step. The contents are strained through six layers of gauze into a 300 cc. salvarsan tube (fitted with a rubber tube and a clamp) and allowed to settle for one hour. The supernatant fluid is poured off, leaving 50 cc. in the tube to ensure

against pouring out any ova. The contents are then mixed, water is added to fill the tube, and the mixture is allowed to settle for one-half to one hour. This step is repeated twice and, if at the end of the third washing a large amount of sediment is still left, the foregoing procedure is repeated after straining the sediment through twelve layers of gauze.

For microscopic examination, the sediment from the salvarsan tube is drawn into a 20 cc. test tube and allowed to settle for 10 minutes. A sample is then drawn from the bottom of the tube with a capillary pipette and spread uniformly over most of a glass slide. The smear should be thin enough to allow use of high dry power of the microscope, if necessary, although the mature and immature eggs are visible and easily found under the low dry objective and 5x ocular lenses.

A mature ovum is brown or yellowish brown, but it may also be colorless, containing an active miracidium which occupies approximately three-fourths of the egg space. The space between the embryo and the shell contains cilia and a fluid with fine granules and mucoid secretions which are usually present. In a few cases, we saw doubled up active miracidia, completely filling the egg shell. Since these eggs were smaller than normal mature eggs, it seems that some factor probably interfered with the normal stretching and enlargement of the shell during the growing period. Mature ova vary considerably in size and shape; from 74 to 106 microns (av. 89) in length and 55 to 80 (av. 67) in width. The ratio between the width and length is variable; occasionally round eggs with mature active miracidia may be found but the usual shape of a mature ovum is oval. The miracidium, when relaxed is pear-shaped, lying in the long axis of the egg, the anterior end being more pointed because of its truncated, cone-shaped head. Its body, however, may assume various shapes caused by the wiggling, contracting activity of the embryo in the egg. Small particles of debris and mucus stick to the outer surface of the shell, usually forming a thin coat, but when they are thickly packed a ragged and irregular appearance to the outline is noted. The smooth thin shell, however, is clearly visible under the surface mucoid layer if examined under high power.

Of the large number of *S. japonicum* ova observed we saw a spine in only a few. If present, the spine is small and most inconspicuous.

Observations were also made on eggs in the intestinal tissues of dogs. Of 700 immature eggs from the intestinal walls of two dogs, 36 (5 per cent) were found to possess spines. (No attempt was made to alter the position of the eggs.) Only 5 (1.6 per cent) of 307 mature eggs showed spines; these were smaller and less conspicuous in comparison with the larger ones seen in immature eggs. The majority of the spines seen in immature eggs were found in very young eggs with soft elastic shells. It seems, therefore, that as the egg shell enlarges, the spine becomes smaller or may be completely obliterated. Faust and Meleney[5] found that all the mature eggs from Japanese sources exhibited an abbreviated spine, whereas it has been the opinion of many observers in China that eggs of *S. japonicum* from Chinese sources lack a spine. Faust and Meleny, however, have found spines in eggs of *S. japonicum* from China, but they were not as clearly demonstrable as in Japanese eggs. The spines of eggs from Leyte, although sometimes observable, were absent or apparently absent in such a large percentage that it seems probable that the ova observed by us are similar to those found in China.

Viable immature and degenerating non-viable ova appeared not infrequently in stools. They varied greatly in shape and in size, but were smaller than mature ova. As in the mature egg, a mucoid-debris layer may adhere to the egg shell; in some eggs it is loosely distributed while in some it forms a thick compact layer. Immature ova are yellow, brown, or dark brown, while dead eggs are dark, often almost black. Vogel[14] gives a detailed description of the morphology of the developing schistosome egg.

The diagnostic or pre-treatment stools may have only developing, yellowish, immature eggs, or both immature and mature, or sometimes only dead ones, or a combination of all three. Some of the immature eggs apparently die during the developmental stage, for, in some patients, dead eggs are found along with immature live ova. In one case, degenerating eggs were found over a period of 17 days before a few mature eggs were detected. In patients receiving treatment, immature and mature ova with active miracidia may be found in the stools for a period of at least 20 days, and, thereafter, degenerate ova may be found.

Other diagnostic techniques were tried to detect schistosome ova.

Direct smears are satisfactory if the infection is heavy or if mucus particles are present in the stools. It is in these particles that eggs are likely to be found in smears. Direct smears do not detect as many positives as can be found by the sedimentation technique. For example, 15 known positive stools were examined by direct smear and the sedimentation method described. Four smears from each stool prepared according to each method were examined. By the direct method, only eight stools were positive and a total of 54 ova were found. By the sedimentation method, all 15 stools were positive, and a total of 474 ova were counted. Flotation methods (using 33 and 44 per cent zinc sulphate) and de Rivas acid-ether concentration techniques were tried with the sediment from the salvarsean tubes, but they did not further concentrate the ova. The eggs either were distorted, killed, or did not float. With the sedimentation technique described, the eggs retain their normal morphology and the miracidia remain viable. In simple centrifugation, regardless of the speed used, not enough of the fine fecal particles is discarded since they are carried down with the sediment.

VIII. TREATMENT

Trivalent antimony in the form of fuadin was used in the treatment of the 75 cases analyzed in detail. This was administered intramuscularly as a 6.3 per cent solution of the drug dissolved in distilled water. The dosage schedule was as follows: 1.5 cc. on the first day; 3.5 cc. on the third day; 5 cc. on the fifth and alternate days thereafter until a total of 40 cc. of the drug (0.340 gram antimony) had been given. No reactions, local or general, to the drug were observed in the dosage employed in this series.

Clinical response to treatment. The evaluation of the effect of treatment on the natural course of schistosomiasis is difficult, as no immediate effect on the fever and symptoms following the institution of chemotherapy was noted; however, improvement in symptoms and subsidence of fever in many patients was observed later during the course of treatment or soon after it was completed. The evaluation of symptoms, however, is difficult and since, with two exceptions, the patients exhibited fever for variable periods of time prior to treatment we selected this as a possible means of measuring response to therapy. The duration of fever prior to therapy was compared with its duration

following the institution of therapy, as illustrated in Table VII. It was postulated that if a uniform temperature response was obtained, irrespective of the duration of fever prior to therapy, it would indicate that therapy exerted some measurable effect. Examination of Table VII indicates that there was a uniform response of the fever in 63 of 72 patients. The duration of fever and symptoms prior to institution of treatment varied from 1 to 10 weeks. Following the institution of therapy, the temperature in 13 cases reached a normal level during the second week, in 39 during the third week, and in 11 during the fourth week. Concurrently, the symptoms also improved and many patients felt well. In others, mild complaints continued. In moderately severe and severe cases, the upper abdominal tenderness lessened markedly or could no longer be elicited, and the enlarged liver and spleen receded. In 7 patients the temperature remained slightly elevated, although symptoms had improved. In 2 cases no improvement was noted during the period of observation of 25 and 31 days, respectively, after therapy was started.

In this series of cases, we believe the evidence cited above suggests that treatment with fuadin was causally related to subsidence of fever, amelioration of symptoms, and recession of physical manifestations.

Post-treatment results. At the time of writing, preliminary post-treatment studies on 110 cases, including 24 of the 75 cases subjected to special study, are avilable. Each patient was treated with 40 cc. of 6.3 per cent fuadin solution (0.340 gram of antimony), according to the schedule outlined above. The results are summarized briefly here. Complete data will be presented in a subsequent report.

The total period of observation varied from 10 to 21 weeks after the onset of symptoms. Treatment was started in the first to the ninth week of symptoms. Post-treatment observations covered a period of from 7 to 15 weeks.

Pre-treatment stool examinations showed mature ova of *S. japonicum* in 95 cases, immature ova in 12, of which 4 eventually showed mature ova. In 3 cases, treatment was begun on clinical evidence only, namely, on the presence of characteristic symptoms, eosinophilia, and history of exposure; ova were never demonstrated in the stools, although characteristic intestinal nodules were found on sigmoidoscopic examination in one patient.

Following treatment, approximately half of the patients complained

of residual symptoms of fatigue, upper abdominal discomfort, cramps, and headache of varying degree and frequency. In many instances, however, these symptoms subsided within two to three weeks after treatment was completed. Of the 110 patients who were followed from 4 to 8 weeks after completion of the course of fuadin outlined above, mature viable ova* were demonstrated in the stools of 19, or 17.2 per cent, before their evacuation from Leyte. It is probable that more of these patients will be found to have viable ova in their stools when they are studied for longer periods of time in the United States. Further experience with antimony in the treatment of schistosomiasis indicates that the regimen outlined above was probably not sufficiently intensive.

IX. DISCUSSION

From the standpoint of prevention of schistosomiasis japonica, it is obvious that utmost caution should be observed to prevent contact of the skin with fresh water in an endemic area, for even momentary contact may give sufficient time for the free-swimming cerceriae to attach themselves. This is well illustrated in the case of the two patients cited (Section III), who contracted the disease while merely washing their hands in a fresh water stream.

The latent period, for reasons as yet unknown, varies greatly which, with the variability in the intensity of clinical symptoms, allows no ground for excluding the disease when the time limits of the latent period, as found in the present series of cases, has been exceeded. This applies, especially, to very mild cases in which symptoms may begin insidiously and also to the asymptomatic cases.

The diagnosis of schistosomiasis japonica in patients exhibiting characteristic symptoms is easy. When the onset is acute with a spiking daily elevation of fever, headache, urticaria, cough, upper abdominal pain, generalized aches and pains, and a stiff neck, together with eosinophilia, the picture is classical. Known exposure completes the clinical evidence. The demonstration of the characteristic ova in the stool confirms the diagnosis. In acute cases, however,

* Captains O. H. Graham, Sn.C., and M. S. Ferguson, Sn.C., Captain F. B. Bang, M.C., and 1st Lieut. N. G. Hairston, Sn.C., of U. S. Army Malaria and Research Units cooperated in the studies of the stools.

the stiff neck may lead to a preliminary diagnosis of meningitis, the pulmonary symptoms to one of bronchitis, asthma, or even pneumonia, and the neruological manifestations to suspicion of some intracranial lesion. The diagnosis of the disease in mild cases or in patients who also have other acute disease may be very difficult indeed. The mild malaise and fatigability, with slight headaches and occasional aches and pains, anorexia, indigestion, and weight loss are symptoms which are relatively common among troops stationed in the tropics and may lead to the diagnosis of psychoneurosis. In many patients admitted to the hospital with infectious jaundice, or because of amoebic dysentery, or for study of obscure eosinophilia, it has been difficult at times to sort out the separate disease entities and to make the diagnosis of schistosomiasis. The demonstration in stools of ova of hookworm, strongyloides or ascaris (which are common parasites in this area), has presented added difficulties, since these ova are easily found and may be discovered before schistosomiasis is suspected. In such cases, eosinophilia may be of no assistance at all because of its variability or occasional absence in schistosomiasis and because of its presence in the other parasitic infestations mentioned.

Confirmation of the clinical diagnosis by demonstration of ova in the stools may be tedious and time-consuming. As many as 15 examinations covering a period of 2 to 3 weeks have been necessary in several of the mild cases before ova have been demonstrated. Rarely, however, have ova not been found in stools of individuals presenting symptoms sufficiently characteristic to make one suspect the disease. In such cases, the sigmoidoscopic examination may reveal characteristic pseudo-tubercles containing nests of ova.

In patients with asymptomatic schistosomiasis, who came from organizations in which the disease was present in typical form and who were referred because eosinophilia had been found on routine survey, long continued search of the stools for ova was sometimes necessary. Nevertheless, in several such cases ova were found in the first stool examined.

Involvement of the central nervous system is of unusual interest. On the basis of available reports of infections with *S. mansoni* and *hematobium*, it appears that such involvement is more common, at least in the initial stage of the disease, in schistosomiasis japonica.

The clinical symptoms varied greatly in severity, a finding which for purposes of description and study led to a division into severe, moderately severe, mild, and asymptomatic groups. The characteristic symptomatology observed in this series corresponds closely to the description given by Faust and Meleney[5], by Kastein[6], and by Egan[7] in their case reports, and corresponds also to the symptoms noted in schistosomiasis mansoni described by Pons[15] in Puerto Rico. Photophobia, a prominent symptom in *S. mansoni* infections was not, however, observed in this series. The one prominent symptom noted in this series, not heretofore commented on, was the stiff neck brought out especially on lateral rotation of the head.

In the beginning of this study, cases of moderate severity were comparatively more frequent, but as time went on the relative incidence of this type decreased as more mild and asymptomatic cases were admitted. This is well illustrated by comparing the severity of the disease in the first 75 cases with that in the total 337 cases observed up to the present time. Of the former, 41 (54 per cent) were classified as moderately severe, 30 (40 per cent) as mild, and 4 (6 per cent) as severe. In three months' time the general picture had changed and was marked by a relative increase of the mild form of the disease and the discovery of the asymptomatic cases. Of the 337 cases observed to date, 21 (6.9 per cent) were severe, 123 (36.5 per cent) were classified as moderately severe, 168 (49 per cent) as mild, and 25 (7.6 per cent) as asymptomatic. It should be noted that the incidence of the severe form has remained about the same.

X. SUMMARY

1. 337 cases of schistosomiasis japonica in United States Army troops in the Philippine Islands have been studied. The first 75 consecutive cases have been analyzed in detail.

2. The data presented include observations on exposure, epidemiology, latent period, characteristic symptomatology and physical findings, eosinophilia, a special modification of the sedimentation method to demonstrate ova in the stools, early clinical response to treatment, and a brief summary of post-treatment results thus far available in 110 cases.

CHART 1, CASE #45

(Schistosomiasis japonica, acute, moderately severe)

White male, age 20, admitted to the hospital 25 January 1945.

Chief complaints: Severe chills, fever, malaise, headaches, and abdominal pain of about 18 days' duration.

Past history: Unrelated to present illness.

Present illness: This soldier swam in a stream known to be infested with cerceriae 6 times between 6 and 18 December 1944. After each swim a sensation of itching and burning of the skin was felt and lasted about thirty minutes. On 7 January 1945, fever, headache and heavy dull upper abdominal pain began and he was admitted to the hospital 9 January 1945. Physical examination was normal; temperature varied between 98 and 101 degrees but gradually subsided; his symptoms abated and he returned to duty on 16 January 1945 with a diagnosis of probable abortive dengue. After discharge, however, he continued to have slight evening fever accompanied by severe headaches, anorexia and upper abdominal pain, followed by soreness and stiffness of his neck, and a dry cough. On 22 January 1945, a chill and severe stabbing pains in the chest occurred. He was admitted to this hospital 25 January 1945. He complained of headache, cough, chest pains, generalized aching, severe upper abdominal pains, anorexia and constipation.

Physical examination: T. 102, P. 100, R. 24, B.P. 115/75. He appeared acutely ill and thin, having lost 12 pounds of weight in the past 2 weeks. Some shortness of breath and a frequent dry hacking cough were noted. The skin was clear, the eyes, ears, mouth, nose and throat were normal. Lymph nodes were not enlarged, the heart and lungs were normal. The abdomen was flat, and the epigastrium was tender to palpation, the liver could be felt 2 centimeters below the costal margin and was quite tender. The spleen was not palpable. The neurological examination was normal. The white count on 25 January was 9,050 with 8 per cent eosinophiles. X-ray of chest on 26 January was read as normal.

Clinical course: A high spiking temperature with daily chills, fever and sweats continued. On 27 January, the leucocytes were 11,000, the eosinophiles 12 per cent. On 28 January 1945, generalized urticaria and angioneurotic edema around the eyes and on the dorsum of the hands developed. His appetite was poor; he complained of a continuous dull heavy ache across the upper abdomen, more definite on the right with marked pain and tenderness in the epigastrium. His cough was frequently paroxysmal, though no abnormal signs were found on examination of the chest. Chest pains were not affected by cough or respiration; they tended to alternate from side to side and were sharp and aching in character. His headaches were severe and occurred chiefly in the evening at the height of his spiking fever. He complained frequently of soreness and stiffness of the neck, especially on lateral rotation of the head. On 30 January, stool examination was negative, the leucocytes were 11,650, the eosinophiles 6 per cent. On 2 February, stool was positive for ova of *Schistosoma japonicum*. On 6 February, the leucocytes were 16,500, the eosinophiles 15 per cent. His course continued unchanged from

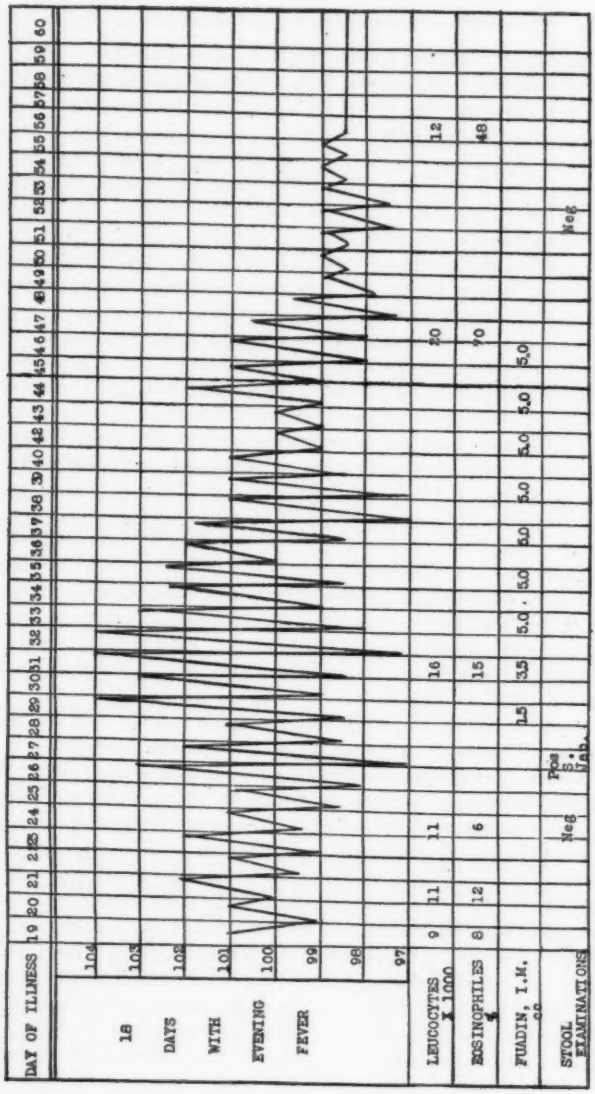

CHART NO. 1. CASE NO. 45. SCHISTOSOMIASIS JAPONICA, ACUTE, MODERATELY SEVERE

the time of admission on 25 January 1945 until 14 February 1945, although treatment with fuadin intramuscularly was begun on 3 February 1945. He lost 20 more pounds weight during this three week period, making a total weight loss of 32 pounds. On 14 February 1945, a marked improvement in his symptoms began, his appetite improved and gradual gain in weight was noted. His temperature, though lower, was still between 100 and 102 degrees each evening. The following day, his white count was 20,000, the eosinophiles 70 per cent. On 23 February 1945, his temperature reached normal and, thereafter, improvement was rapid. The liver edge, though palpable, was no longer tender, epigastric tenderness was only slight, and occasional mild episodes of coughing, transient chest pain and upper abdominal discomfort persisted. Small urticarial lesions appeared from time to time on the abdomen. On 1 March 1945, except for occasional mild scattered aches and pains he was asymptomatic. On 3 March, the white count was 12,000; the eosinophiles 48 per cent.

Summary: The latent period in this case was calculated to be 32 days from initial exposure to infested water to the onset of the acute illness, suggesting dengue, symptoms of which subsided sufficiently to lead to discharge from hospital. Mild symptoms continued, however, culminating after several days in a chill and aggravation of symptoms. This initial acute illness suggesting dengue at the onset is discussed in Section V. The clinical course in this patient was typical of what we have termed the moderately severe form of the disease. His temperature was elevated each evening from the 7th of January to 23 February 1945. Treatment was instituted at the end of the fourth week of symptoms, and was completed 3 days before his temperature returned to normal. The total white blood cell count and percentage of eosinophiles initially were only slightly elevated; both gradually increased during the acute phase and did not drop with clinical improvement. This patient eventually relapsed and is included in the 110 cases treated with fuadin, summarized in Section VIII.

CHART 2, CASE #4

(Schistosomiasis japonica, acute, moderately severe)

White male, age 22, admitted to the hospital 6 January 1945.

Chief complaint: Fever, chills, weakness, chest pain and headaches for three weeks.

Past history: Soldier had spent 6 months on a tropical island where malaria was endemic. However, clinical malaria had never developed and routine suppresive atabrine had been taken.

Present illness: From 10 to 15 November 1944, this soldier waded and swam in rivers and swamps now known to be infested with cerceriae of *S. japonicum.* Itching of his skin was never noted. He remained asymptomatic until 17 December 1944, when feverishness, headaches, anorexia, generalized aches and pains, especially of the chest, and a non-productive hacking cough developed. Urticaria was never noted. He was admitted to a hospital 18 December 1944 where he

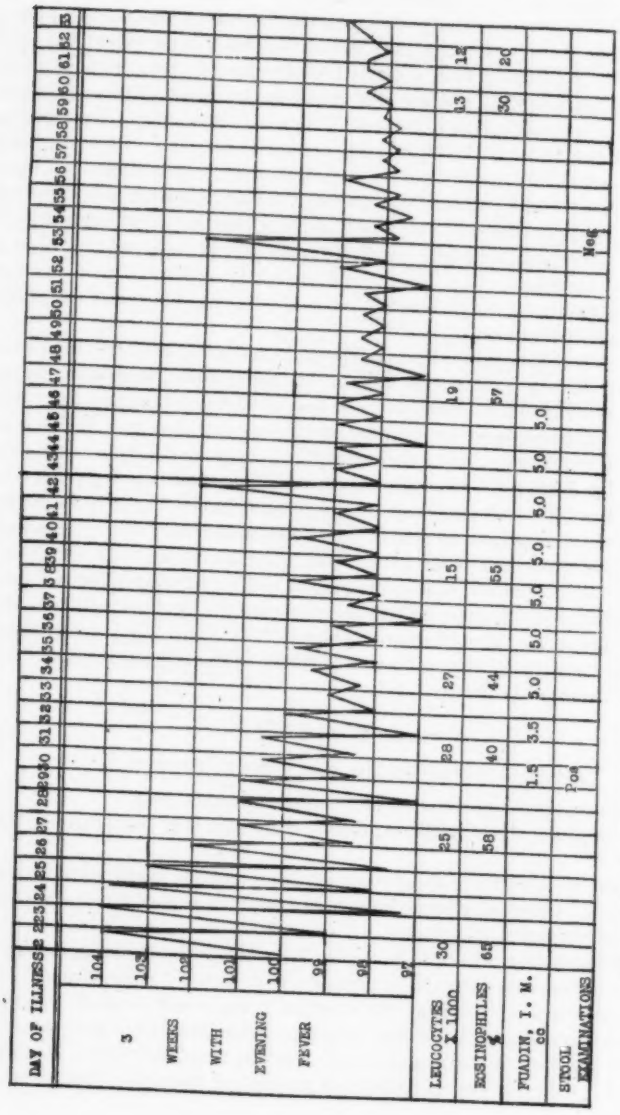

CHART NO. 2. CASE NO. 4. SCHISTOSOMIASIS JAPONICA, ACUTE, MODERATELY SEVERE

continued to have a high spiking fever each evening and a normal temperature each morning. Although numerous smears of the blood were negative for malarial parasites, antimalarial therapy was begun, but was without effect and symptoms continued unabated with cough, chest pain, anorexia, evening fever, headache and marked weakness. On several occasions his neck was sore and stiff. On transfer to this hospital 6 January 1945, he had lost 30 pounds and was complaining of the symptoms enumerated. During this entire period he invariably felt better in the mornings.

Physical examination: T. 101.8, P. 96, R. 20, B.P. 105/68. He was pale, sallow, with evidence of marked weight loss. The skin, except for scattered epidermophytosis, was normal. There was no general or local lymph node enlargement. The eyes, ears, nose, mouth and throat were normal. He had a dry hacking cough. At the base of the right lung there was dullness and a few scattered fine, moist, and coarse rales were heard. The movement of the diaphragm on the right was limited. The abdomen was flat. The liver was not palpable, but enlarged to percussion, and tenderness, especially on palpation in the mid-epigastrium was elicited. The spleen could not be felt. The neurological examination was normal. The leucocyte count was 30,600 with 65 per cent eosinophiles.

Clinical course: All symptoms continued unabated until the sixth day in hospital, 12 January 1945, when definite spontaneous improvement was noted and his evening temperature rise was less marked. The leucocytes remained high: 25,000 with 58 per cent eosinophiles. His stool was positive, 15 January 1945, for mature ova of *S. japonicum* and treatment with intramuscular injections of fuadin was begun. X-ray of chest 16 January 1945 showed increased peribronchial markings with patchy infiltration at the base of the right lung. He continued to improve rapidly so that by 18 January his temperature was only slightly elevated, and his only complaints were occasional abdominal cramps, some upper abdominal discomfort, intermittent chest pains, slight cough and evening headaches. On 23 January, he was further improved. The physical examination was unchanged except for the fact that the spleen was now palpable and the lungs were clear, except for a few coarse rales at the right base posteriorly. The leucocytes had dropped to 15,700 with 55 per cent eosinophiles. 29 January treatment was completed, after the patient had received 40 cc. of fuadin intramuscularly in 9 doses. He felt well except for weakness, upper abdominal pain, occasional generalized joint aches and pains, and stiffness of the neck. He had gained 6 pounds. His temperature was practically normal. Another x-ray examination of the chest, 1 February 1945, showed marked increase of the peribronchial markings but clearing of the patchy infiltration at the right base. The white count, however, was higher: 19,200 with 57 per cent eosinophiles. Symptoms further subsided, the lungs cleared, the liver was palpable but not tender, and an additional 12 pounds gain in weight was noted. One examination of stool, 8 February 1945, was negative for ova. 17 February the white count had dropped to 12,400 with 20 per cent eosinophiles. When evacuated from the hospital 18 February 1945 he felt well.

Summary: Exposure in this case was limited to four day the latent period as calculated was 26 days. Symptoms extending over 5 weeks were moderately severe and were accompanied by considrable weight loss. Some improvement in his condition was noted prior to institution of treatment; thereafter, he made rapid progress. The eosinophilia in this instance remained high during the third and fourth weeks of the symptomatic phase, then gradually decreased.

CHART 3, CASE #66

(Schistosomiasis japonica, acute, mild)

White male, age 29, admitted to the hospital 12 January 1945.

Chief complaint: Headache, feverishness, stomach ache of two days' duration.

Past history: Unrelated to present illness except that he had urticaria occasionally during the year prior to arrival on this island. Family history is negative for allergic manifestations.

Present illness: This soldier was assigned to a malarial control detail 19 November 1944, which necessitated wading daily in swamp water well over his shoe tops until 30 November 1944. On 2 occasions, 23 and 24 November 1944, he swam in a river now known to be infested with cerceriae of *S. japonicum*. Itching of the skin did not follow contacts with fresh water. He was asymptomatic until 10 January 1945, when headache, fever, nocturnal cough, malaise, mild constant epigastric pain and discomfort began abruptly. The next day he noticed scattered urticaria and wheals over the trunk, thighs and the palms and dorsum of both hands. His symptoms persisted, and on 12 January 1945 he was admitted to the hospital.

Physical examination: T. 99.8, P. 98, R. 20, B.P. 110/75. He appeared thin and though his appetite had been good, he had lost 15 pounds in the preceding month and a half. The eyes, ears, nose and throat were normal. There was no lymph node enlargement. Scattered wheals 1 to 3 cm. in diameter were noted over the arms, trunk and thighs. An occasional dry hacking cough was heard. The heart and lungs were normal. The abdomen was flat, there was definite slight epigastric tenderness to percussion and on deep palpation. The liver and spleen were enlarged, and tenderness under the right costal margin was elicited. The neurological examination was normal. The white count, 15 January 1945, was 8,300 with 23 per cent eosinophiles.

Clinical course: The temperature was elevated in the evening to 100 to 101 degrees. Malaise, headache and epigastric discomfort continued, but on the whole he felt quite well until late afternoon. His appetite remained good. Stools were positive for ova 16 and 17 January 1945, six days after onset of symptoms. 18 January leucocytes were 10,000 with 26 per cent eosinophiles. Treatment with intramuscular injections of fuadin was begun 19 January 1945. X-ray examination of the chest 22 January 1945 was interpreted as normal. 24 January 1945 he complained of transient stiff sore neck, especially severe when he rotated his head. This lasted 24 hours. 25 January 1945 leucocytes were 13,400 with 63

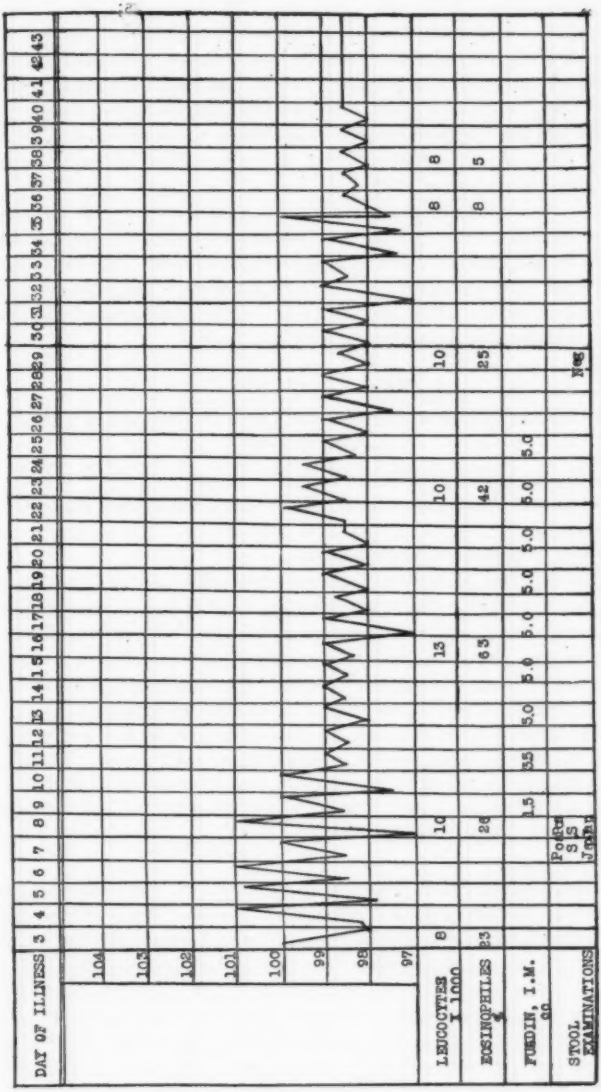

CHART NO. 3. CASE NO. 66. SCHISTOSOMIASIS JAPONICA, MILD

per cent eosinophiles. 25 January 1945, mild transient sharp pain in his left chest developed. Treatment was completed 4 February 1945, after he had received a total of 40 cc. fuadin intramuscularly in 9 doses. 4 February 1945, the temperature was normal. The epigastric pain and tenderness could not be elicited 6 February 1945. 7 February 1945, the stool was negative for ova and the leucocytes were 8,100 and the percentage of eosinophiles had dropped to 8 per cent; 17 February the count was 8,040 with 5 per cent eosinophiles. He was evacuated from this island 18 February 1945.

Summary: This case represents the mild form of the disease. The latent period was 52 days; i.e., from first exposure to infested water to onset of first symptoms. Ova of *Schistosoma japonicum* were found in his stool on the first examination, 7 days after onset of symptoms or 59 days after exposure. The eosinophile count rose and dropped quickly. His rapid clinical improvement following the institution of therapy suggests that treatment was related thereto.

CHART 4, CASE #51

(Schistosomiasis japonica, acute, severe, with involvement of central nervous system)

White male, age 21, admitted to the hospital 3 February 1945.

Chief complaint: Weakness, malaise, hives, fever, abdominal pain of about a week's duration.

Past history: Unrelated to present illness.

Present illness: This soldier swam 12 times between 6 and 24 December 1944, in a river now known to be infested with cerceriae of *S. japonicum*. No itching was noted after swimming. Feverishness and fatigue with evening headaches began 20 January 1945. 26 January, generalized urticaria with angioneurotic edema appeared around the eyes and mouth. He complained of slight itching and swelling of his tongue, of severe headaches, marked upper abdominal pain and cramps, and all his muscles and bones seemed to ache. He had a dry hacking cough each evening accompanied by transient sharp chest pains. At night on several occasions he was short of breath and seemed to have mild asthma. His symptoms persisted, and he was admitted to the hospital 3 February 1945. 1 February, two days prior to admission, the leucocytes were 20,000 with an eosinophilia of 80 per cent.

Physical examination: T. 101, P. 96, R. 26, B.P. 120/75. He looked acutely ill, seemed vague and unable to concentrate on questions asked him. He continually asked the examining officer where he was, then would answer his own question. He stared about and appeared worried and somewhat apprehensive. His neck was sore and motion was limited, especially when lateral rotation was attempted. His eyes, ears, nose, mouth and throat were normal. There was a fading area of angioneurotic edema on the upper lip and scattered urticaria over his trunk. The posterior cervical lymph nodes were enlarged. The heart and lungs were normal. The liver was enlarged and the tender edge was easily palpable below the

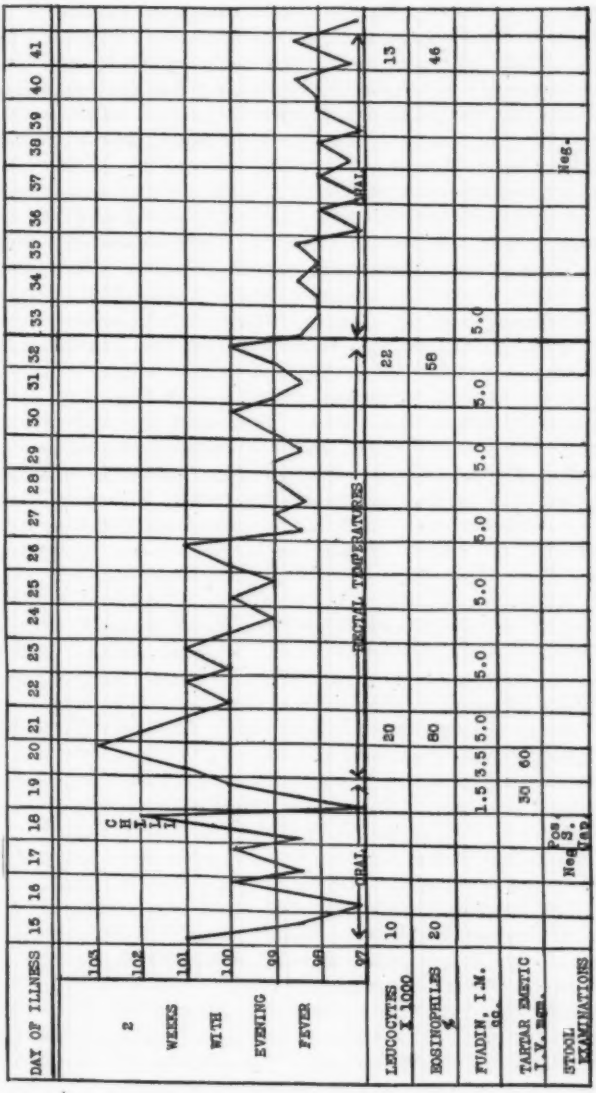

CHART NO. 4. CASE NO. 51. SCHISTOSOMIASIS JAPONICA, ACUTE, SEVERE, WITH INVOLVEMENT OF CENTRAL NERVOUS SYSTEM

costal margin. There was epigastric tenderness to percussion and palpation The spleen was not palpable. The neurological examination was normal.

Clinical course: His symptoms continued and he remained vague and listless but oriented. Cough, giant urticaria, headaches and upper abdominal pain persisted. His temperature was elevated in the evening. The stool was negative 5 February, but on 6 February, 14 days after onset of symptoms, ova of *S. japonicum* were found in his stool and treatment with fuadin intramuscularly was begun. That evening he appeared weak and somewhat lethargic, but his physical and neurological examinations were unchanged. He was given intravenous normal saline in 5 per cent dextrose in the evening, but before he received 100 cc. a very severe shaking chill with abdominal cramps and marked nausea and vomiting developed. The intravenous injection was discontinued at once. On the morning of 7 February 1945, his condition appeared unchanged except that he staggered and fell in attempting to get out of bed. That afternoon he suddenly began to have almost constant clonic spasms of his arms and legs with tonic flexion of the elbow, wrist joints, and extension of the legs. Though not stuporous or comatose, he did not respond to questions or appear to hear or understand them. He was greatly agitated and emotionally disturbed. Neurological examination revealed: head and eyes turned toward the right, though he occasionally moved them to the central position. Marked flexion and adduction of arms with flexion of wrists and extension of legs with increased muscle tone was found. Marked resistance to passive motion of all extremities was elicited, as well as bilateral positive Hoffman and Babinski signs and bilateral sustained ankle clonus. Deep reflexes were all hyperactive. There was, however, no actual paralysis as he could freely move his extremities. He became incontinent of urine and feces. His temperature rapidly rose to 103 degrees, rectally. In addition to intramuscular fuadin, he was given a total of 90 mgm. of tartar emetic intravenously. A lumbar puncture, 8 February 1945, revealed normal spinal fluid: the dynamics were normal, Pandy negative, no cells, and protein not increased. For the next 7 days his condition remained much the same. Though vaguely oriented, he was violent, abusive, crying out wildly and incoherently, and then would burst forth into song. He was restless and emotionally uninhibited. The picture was not unlike that of acute encephalitis with severe associated personality changes. The generalized weakness and hypertonicity of the muscles of his extremities localized to those on the right side. The deep reflexes were hyperactive; there was sustained ankle clonus and Hoffman's and Babinski's signs were positive. He was gradually more en rapport with his surroundings and more emotionally controlled. 16 February 1945, he became afebrile; and 17 February 1945, he was continent of feces. By 20 February 1945, it was possible to take his temperature by mouth without his biting off the end of the thermometer, and he became continent of urine. Treatment with fuadin was completed 21 February 1945, at which time the leucocytes were 22,500 with an eosinophilia of 58 per cent. At this time, his neurological examination was typical of that of a patient with a right hemiplegia. Mentation seemed normal; he was alert and clever in conversation and his temperature was normal. Gradual im-

provement continued, the peripheral neurologic signs slowly decreased and, when evacuated to the zone of interior 11 April 1945, only slightly exaggerated superficial reflexes of the lower extremities with faint bilateral Babinski responses could be elicited. The white blood cell count on 2 March 1945 was 13,000 with 46 per cent eosinophiles; on 12 March it was 9,250 with 26 per cent eosinophiles. The first post-treatment stool examination on 28 February showed immature ova only and seven subsequent examinations done at intervals of 5 days, the last on 4 April, were negative.

Summary: This patient was one of two who developed severe neurologic complications, evidence of which appeared 17 days after the onset of the usual acute symptoms of the disease. The latent period was 45 days. Ova were found in the stools 14 days after the onset of symptoms or 59 days after the first exposure to infested water. The onset of the cerebral symptoms and peripheral neurologic signs indicating extensive involvement was so abrupt that it is difficult to visualize the changes as being due solely to deposition of ova. Since there was simultaneously rather extensive urticaria and angioneurotic edema, the possibility that cerebral edema played some role was considered. The eosinophilia increased during, but dropped after, treatment and was still elevated two months later, although stools remained negative.

The very excellent result clinically in this patient's condition was most striking and is quite similar to Egan's[7] case 5, in which the mental disturbances and neurologic signs gradually disappeared.

BIBLIOGRAPHY

1. Garrison, P. E.: The Prevalence and Distribution of the Animal Parasites of Man in the Philippine Islands with a Consideration of their Possible Influence upon Public Health. Philip. Jour. Sci., **III:** B (1908) pp. 191–210.
2. Africa, C. M. and Garcia, E. Y.: The Distribution of Schistosomiasis Japonica in the Philippines. Philip. Jour. Pub. Health 2 (1935) pp. 54–62.
3. Tubangui, M. A., and Pasco, A. M.: Studies on the Geographical Distribution, Incidence and Control of Schistosomiasis Japonica in the Philippines. The Philip. Jour. Sci., Vol. 74, pp. 301–327 (April) 1941.
4. Data supplied by Capt. O. H. Graham, Sn.C., Capt. M. S. Ferguson, Sn.C., Capt. F. B. Bang, M.C., and 1st Lt. N. G. Hairston, Sn.C., of U. S. Army Malaria and Research Units.
5. Faust, E. C. and Meleney, E. H.: Studies on Schistosomiasis Japonica. A monograph series. No. 3, Amer. Jour. of Hygiene, Baltimore, Md., 1924.
6. Kastein, J.: Beobachtungen von gehauften auftreten von "Schistosomumjaponicum"—erkaukungen in Shanghai. Arch. F. Schiffs u. Tropen Hyg., **36:** pp. 1–4, 1932.
7. Egan, C. H., Lt. Com., R.N.: An Outbreak of Schistosomiasis Japonica. J. Roy. Nav. M. Ser., **22:** pp. 6–8, 1936.

8. FAUST, E. C. AND HOFFMAN, W. A.: Studies on Schistosomiasis Mansoni in Puerto Rico. I–III Puerto Rico Jl. Pub. Health and Trop. Med., **9:** 154, 228, 1933; **10:**1, 1934.
9. Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases by Richard P. Strong. Vol. 2, pp. 1427, 1942, the Blakiston Co., Philadelphia.
10. HUNT, A. R., Lt. (MC) USNR: Schistosomiasis in Naval Personnel. A Report of 16 Cases. In press.
11. GARCIA, E. Y., NAVORRO, R. J., AND BAUTISTA, L.: A Case of Cutaneous Schistosomiasis involving Schistosoma Japonicum eggs. Acta. Med. Philip., I: pp. 339–345, 1939–1940.
12. JOHNSON, A. S., JR., MAJ., M.C., AUS; BERRY, M. G., LT. COL., M.C., AUS: Schistosomiasis—A Paper Presented to Leyte Med. Soc., 8 March 1945.
13. VITUG, W., M.D., CRUZ, J. R., M.D., AND BAUTISTA, L. D., M.C.: Schistosomiasis Involving the Brain: Two Case Reports. Jour. Philip. Med. Assoc., **21:** pp. 291–298, June 1941.
14. VOGEL, HANS: Ueber Entwicklung, Lebensdauer und Tod der Eier von Bilharzia japonica imm Wirtsgewebe. Deut. Trop. Ztschr. **46:** 57–69 and 81–91. 1 and 15 February 1942.
15. PONS, J. A. Studies on Schistosomiasis Mansoni in Puerto Rico. V. Clinical Aspects of *S. mansoni* in Puerto Rico. Puerto Rico Jour. Pub. Health and Trop. Med., **XIII:** No. 2, December 1937, pp. 171–254.